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THE LIVER IN FERROUS SULFATE POISONING*

A Report of Three Fatal Cases in Children and an Experimental Study

MICHAEL A. LUONGO, M.D.,† AND S. STEFAN BJORNSON, M.D.‡

BOSTON

CASES of toxicity from ferrous sulfate have been reported sporadically for two centuries. Revival of interest in acute iron poisoning stems back, however, to the report of Forbes[1] in 1947, which included a description of clinical symptoms, pathological findings and an experimental study demonstrating the toxicity of large doses of iron compound. Since that time, many reports of both fatal and nonfatal poisoning have appeared, nearly all of which followed the accidental ingestion of ferrous sulfate tablets by children. In addition interest in the role of iron and its compounds and metabolites in human siderosis, hemosiderosis and cirrhosis of the liver has recently revived.

Medicinal iron is ordinarily administered as ferrous sulfate in tablets or capsules. Of importance, as far as accidental poisoning in children is concerned, is the fact that many preparations are in the form of attractively colored tablets coated with sugar and chocolate. A child confronted with such a "confection" may ingest what, in terms of ordinary therapy, is a massive dose. Since there is some ignorance of this danger even among physicians, most lay people consider ferrous sulfate and other medicinal iron preparations harmless and take no special precaution to protect children from easy contact. The 3 fatal cases reported below occurred within a period of two years in a county of approximately 1,000,000 people. It is interesting that in each case the mother had recently been taking a daily dose of ferrous sulfate prescribed during pregnancy.

Our interest in iron poisoning arises out of two considerations. The first is the observation that some physicians do not yet recognize that common preparations of iron, particularly ferrous sulfate, may in accidentally ingested large doses cause poisoning in children. Secondly, our observations of the liver damage, both in fatal human cases and in experimental iron poisoning in animals, indicate a basic pattern of hepatic injury that might shed light on the pathogenesis of such conditions as siderosis and some forms of cirrhosis of the liver.

There has been little agreement in published theories about the nature of the hepatic damage in fatal human cases and even disagreement about the changes in laboratory animals. Forbes,[1] in his report of 2 cases, described degenerative changes that varied from cloudy swelling to complete necrosis. Some liver lobules had entirely disappeared whereas in others only the central cells remained. Thomson, in 1947[2] and in 1950,[5] reported 8 cases, with 3 deaths. In these cases, he made note of no particular histologic damage in the liver. Spencer[4] presented 8 cases, 4 of which were fatal; the only change noted in the liver was cloudy swelling. Foucar, Gordon and Kaye[5] described a case, studied at autopsy, of a twenty-six-year-old man who ingested 114 gm. of ferrous sulfate. The liver showed varying degrees of parenchymatous degeneration, without mention of particular distribution of injury. Smith et al.[6] reported an autopsied case of iron poisoning with degeneration of the central four fifths of the hepatic lobules. Duffy and Diehl,[7] in a study of 3 cases, with 1 death, observed cellular swelling without necrosis. Swift, Cefalu and Rubell[8] described 1 death with degeneration of the cells in the central portion of the liver lobules. Smith[9] reported a fatal case showing normal hepatic parenchyma but with iron impregnation of the portal tracts. Invariably, in the fatal cases, edema and necrosis of the gastric mucosa are noted. The changes in the liver frequently described are those of cloudy swelling and focal necrosis. So far as damage in the liver is concerned in the laboratory animal, reports have been inconclusive. In animals subjected to toxic doses of iron preparations Forbes[1] observed cloudy swelling of liver cells and vacuolization of the cytoplasm. Somers[10] found small foci of fatty degeneration and some necrosis of the peripheral portions of hepatic lobules that were not uniform. Forbes[1] and Prain[11] concluded from their observations that death from ferrous sulfate poisoning is due directly to the cloudy swelling, fatty changes and necrosis in the liver and base this assumption on the idea that a damaged

*From the Department of Legal Medicine, Harvard Medical School.
†Associate in legal medicine, Harvard Medical School; associate medical examiner, Suffolk County, Massachusetts; pathologist, Waltham Hospital.
‡Research fellow in legal medicine, Harvard Medical School; visiting pathologist, Jordan Hospital, Plymouth, Massachusetts.

liver is not capable of maintaining a detoxifying process of iron in the presence of continuing absorption. Smith[8] postulated that ingestion of massive doses of iron compounds breaks down the "mucosal block" of Hahn et al. to promote the formation of apoferritin and ferritin. Ferritin is considered a vasodepressor substance that causes the shocklike state that frequently follows the ingestion of toxic doses of medicinal iron preparations.

Case Reports

Case 1. A 16-month-old Negress was admitted to the hospital on September 22, 1951, at 7:25 a.m. The history was obtained from the mother. Some time before 6 a.m. on the day of admission, the child stood up in bed and took from a mantel shelf a bottle containing numerous ferrous sulfate tablets. The child was discovered by the mother "frothing at the mouth." In the hospital the child was in a shocklike state and was anuric. Cheyne—Stokes breathing followed, and she died in spite of supportive therapy on the next day at 2:20 p.m. A police investigation at the home revealed no containers of drugs or poisons other than that from which the child had eaten an unknown number of ferrous sulfate tablets, prescribed for use by the mother during pregnancy. The child had been in good health until the time of the accidental ingestion of the medicinal iron.

Autopsy showed a well developed and well nourished child without significant external abnormalities. There was a moderate congestion and edema of the lungs. The mouth contained brown-stained mucus and froth. The stomach mucosa showed a dark-brown corrosion that was particularly noticeable in the fundus but was present in all portions. This was most marked in the tips of the rugal folds. The entire wall of the stomach was edematous, being swollen to approximately 1½ times the normal thickness. In some places the rugal pattern was obliterated with deep-brown staining of the mucosa. No ulceration, however, was present. The proximal duodenum disclosed a similar dark-brown discoloration. The jejunum and ileum demonstrated blackening of the tips of the mucosal folds without vascular engorgement. The large intestine was dilated and filled with coal-black, pasty material. The mucosa in the large intestine showed no recognizable abnormality, being only slightly congested. The rectum was filled with similar black, pasty material. The liver was slightly swollen, with a barely perceptible rounding of the edges. The cut surface was yellowish brown, with prominence of some central areas, which stood out as brownish hemorrhagic spots. Otherwise, the gross architecture was normal. No gross abnormality of the kidneys was noted. The brain revealed only slight edema.

Routine sections of formalin-fixed tissues (lung, heart, spleen, kidneys, brain, adrenal glands and pancreas) stained with hematoxylin and eosin showed only nonspecific and moderate changes of congestion and edema, and minimal cloudy swelling of cells. The liver, however, was the seat of significant histologic change (Fig. 1*B* and *C*). In the portal areas the cells were almost completely disintegrated, and those in the central portions disclosed severe cloudy swelling, with loss of ordinary cytologic detail. Only scattered groups of red blood cells and a few inflammatory cells, mostly polymorphonuclear leukocytes, were present about the damaged cells. Iron stains demonstrated a fine deposit of iron, with a definite periportal distribution. Iron stains on sections of kidney, spleen, lung, pancreas, adrenal gland and brain were negative.

Case 2. A 1½-year-old Negro was admitted to the hospital on March 29, 1953, at 1 p.m. The mother stated that the patient, who had previously been in good health, had eaten an unknown number of sugar-coated 0.3-gm. ferrous sulfate tablets that had been prescribed for her. Soon after this, he vomited and became extremely ill. While being transported to the hospital he vomited several times. On admission he was lethargic and listless. The extremities were cold, and the respirations shallow. The stomach was lavaged, and supportive therapy, including fluids, were administered. However, in spite of these measures, respirations gradually became more labored, and the heart sounds of extremely poor quality. The temperature rose gradually to 105.8°F., and the child died on March 30 at 8:45 a.m.

Autopsy disclosed a well developed and well nourished colored boy. The external appearance was quite normal. The mouth was filled with brownish mucus. No external injury was present. The body cavities contained no excess fluid. The thoracic organs, including the heart, great vessels and lungs, were of normal gross appearance, though the lungs showed moderately severe congestion and edema. The esophagus was normal. The stomach contained about 90 cc. of brownish-black fluid. There was deep-brown staining of almost the entire gastric mucosa that extended into the proximal portion of the small intestine, including the duodenum and the first 20 or 30 cm. of the jejunum. The large bowel contained a mixture of gas and black fecal material. No congestion or irritation of the large intestinal mucosa was noted. The liver weighed 295 gm., with slight swelling and rounding of the edges. The cut surface was yellowish brown, with a striking brownish-red mottling somewhat similar to the classic "nutmeg liver" of chronic passive congestion. The spleen, pancreas, kidneys and adrenal glands revealed only slight congestion. The brain showed definite edema, with flattening of the convolutions and almost complete obliteration of the sulci over the parietal areas.

Routine sections of formalin-fixed tissues stained with hematoxylin and eosin were examined microscopically. As in Case 1 there were slight, nonspecific changes in heart, spleen, pancreas, adrenal glands and kidneys. The brain showed moderate edema, and the lungs severe congestion and edema. Sections of the stomach and duodenum demonstrated corrosive changes and congestion of the mucosa; the corrosion was particularly noticeable in the tips of the mucosal folds. Iron stains disclosed a heavy deposit of iron in the mucosa and in the intimal cells lining the submucosal veins. The changes in the liver were striking. A narrow zone of necrosis surrounded all portal tracts. In these necrotic areas the size of the cells was markedly diminished, and the cytoplasm compressed, with loss of nuclear and cytologic detail in general. The necrosis involved approximately 1/5 of the peripheral or periportal portions of the liver lobules (Fig. 1*A*). Fat stains showed a fine fatty vacuolization of the periportal necrotic areas, and iron stains a perceptible deposit of finely dispersed iron in the stained areas.

Case 3. A 1-year-old girl was admitted to the hospital on November 1, 1953, at 6:50 p.m., having passed into coma for no apparent reason at approximately 4:30 p.m. She was first taken to a relief station and thence to the hospital for further evaluation and treatment. There was no history of prior illness. Police who investigated the home found no poisonous substance in the house. The only medicine found was a ferrous sulfate preparation prescribed for the mother, who was 6 months pregnant. Before the sudden collapse and coma the patient had vomited twice. On admission there was a shocklike state with severe acidosis and anuria. The clinical diagnosis was questionable exogenous poisoning. Foam and blood appeared at the mouth and nose, and in spite of vigorous supportive therapy, the patient died shortly after admission.

Autopsy revealed a well developed and well nourished girl with a slight pallor of the skin. No external injury was present. The mouth contained brownish froth and mucus. The significant gross internal findings were restricted to changes in the stomach, intestine and liver. The heart was slightly dilated; the musculature and valves were of normal appearance. The lungs showed moderate congestion and edema. The esophagus was normal. The stomach disclosed brown staining, particularly in the fundus but also in the lower portions. There was no ulceration of the gastric mucosa and no corrosion. There was slight brown staining of the mucosa of the duodenum. The small intestine contained only a small amount of gas and was almost devoid of chyme and fecal material. The large in-

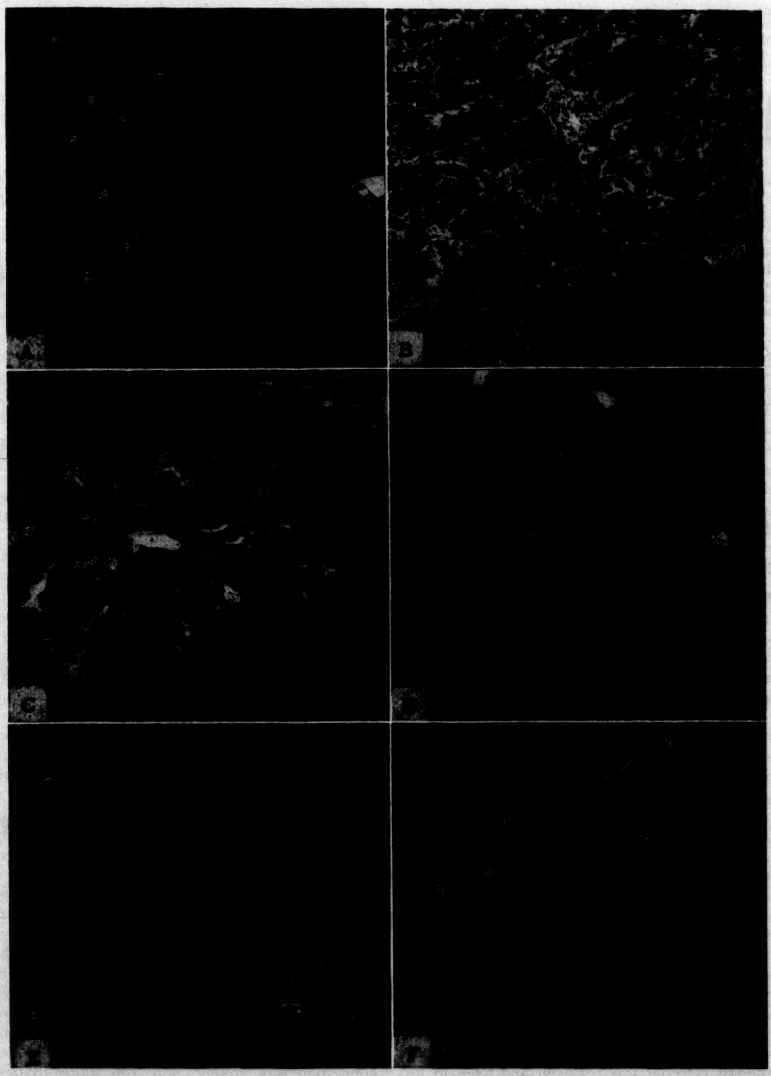

FIGURE 1. *Hepatic Lesions in Ferrous Sulfate Poisoning, Showing a Dark Necrotic Periportal Zone of Necrosis in Case 2, Involving Approximately a Fifth of Each Lobule* (A); *Marked Fatty Vacuolization (Dark Areas) of Periportal Cells* (B) *and Preserved, Relatively Normal Cells in the Central Area about the Central Vein, with a Surrounding Necrotic Zone of Cells* (C) *in Case 1; Section of Liver of Rabbit Twenty-Four Hours after Administration of 1 Gm. of Ferrous Sulfate per Kilogram of Body Weight* (D) — *Dark Areas Represent Low-Power View of Preserved Central Zones, and Light Areas Necrotic Zones; Higher Magnification of Section Presented in* B, *Showing Preserved Central Cells and Necrotic Periportal Cells* (E); *and Fine Fibrosis or Minimal Cirrhosis in Rabbit in Healed Stage Thirty-Five Days after Administration of 1 Gm. of Ferrous Sulfate per Kilogram of Body Weight* (F).

testine, which contained abundant gas, was dilated and covered with specks of black pasty material that were most prominent in the cecum and ascending colon. The rectum was empty. A few small areas of hyperemia were noted in the jejunum and ileum. The liver, which exhibited the most striking abnormality encountered during the autopsy, weighed 340 gm. and had a smooth, thin capsule. The whole organ was light yellowish brown; the cut surface was speckled with barely visible fine hemorrhagic areas. The spleen, pancreas, kidneys and adrenal glands demonstrated only slight congestion. The brain had a normal configuration, with perhaps slight edema. No other gross abnormality was noted.

Routine sections of heart, spleen, pancreas, adrenal glands, brain and kidneys stained with hematoxylin and eosin showed slight nonspecific changes similar to those in Cases 1 and 2. The lungs exhibited patchy areas of hemorrhage as well as severe edema and congestion. Sections of the liver were most noteworthy. There were patchy areas of hemorrhagic necrosis, most of which surrounded portal tracts. However, some were present in both central and mid-zone areas. Fat stains demonstrated striking generalized fatty vacuolization of liver cells whereas iron stains were quite inconclusive, with only a barely perceptible deposit of iron-staining material in necrotic areas.

Experimental Study

The purpose of the experimental study of ferrous sulfate poisoning in animals was to produce, if possible, the hepatic lesions observed in the fatal human cases, particularly the portal necrosis. Other workers had not previously emphasized any particular pattern of liver damage. After the experimental production of severe liver damage, our next purpose was to observe histologically the fate of the lesions to the point of healing.

Materials and Methods

An initial study was undertaken to determine the maximum sublethal dose of ferrous sulfate. Twenty rabbits, weighing between 1700 and 1800 gm., were given a solution of ferrous sulfate by stomach tube before feeding time. The dosage varied from 0.25 gm. to 3.0 gm. per kilogram of body weight. All animals given 2 gm. or more died within a few hours of administration; those given less than 0.75 gm. survived, and those killed at varying intervals after the administration of the dosage showed no pathological changes. From this initial study it was determined that a dosage in the range of 0.75 to 1 gm. per kilogram of body weight produced recognizable necrosis of the periportal areas in the liver, and, in addition, allowed for a sufficient survival of poisoned animals to study the lesions to the point of healing microscopically.

A second experiment was undertaken in which 25 rabbits were given 1 gm. per kilogram of body weight by stomach tube. Six of these animals died within a few hours of the administration of the ferrous sulfate. The remainder survived and were killed at intervals varying from one to thirty-five days. From all animals material was removed and fixed in formalin for histologic preparations. The surviving rabbits were allowed to have their regular feedings, which consisted of compressed pellets of rabbit food (Purina rabbit pellets). Histologic sections were stained routinely with hematoxylin and eosin and Turnbull's ferrous iron stain. Frozen sections were stained with Sudan IV.

Experimental Observations

In all rabbits given toxic doses of ferrous sulfate the gastric mucosa was stained dark reddish brown. The mucosa in animals killed at varying intervals after poisoning by ferrous sulfate reverted to normal in appearance five to six days after the administration of the ferrous sulfate. In general the gross autopsy findings were quite nonspecific. Most animals showed edema and congestion of the lungs when death followed extremely large dosages. In animals surviving toxic, though not fatal, doses the liver had a uniform appearance during the first four days, being a light yellowish brown, with a brown-purple speckling somewhat like that in a "nutmeg liver." In the animals given 1 gm. of ferrous sulfate per kilogram of body weight, though striking gross changes were evident during the first five days, after the first week the healing progressed sufficiently so that no gross alteration in the architecture was discernible. However, the spleen and kidneys invariably disclosed a moderate congestion.

Histologic examinations of sections from stomach and small intestine in animals killed at intervals of one to five days revealed severe congestion of mucosal surfaces, with ulceration of the surface and impregnation of the epithelial cells with iron that varied in degree from animal to animal but was usually striking. There was congestion of the submucosa, without thrombosis of any of the vessels. Iron impregnation of the endothelial cells of the submucosal veins was often demonstrable. After five days the gastric mucosa usually reverted to normal histologically. Histologic examinations of spleen, pancreas and adrenal glands usually showed a moderate congestion without particular abnormality. Sections of livers from rabbits given 0.75 gm. of ferrous sulfate per kilogram of body weight indicated marked congestion, particularly in the portal areas, but no actual necrosis. Those given 1.25 gm. per kilogram of body weight showed severe necrosis of almost the entire liver lobule, with only a few remaining intact central cells about the central veins. In addition to the necrosis there was often considerable infiltration with polymorphonuclear leukocytes in the necrotic areas, which were often mottled with hemorrhage. Rabbits given 1.5 gm. or more per kilogram of body weight died within a few hours, not having survived long enough for the development of characteristic liver lesions. In these animals the liver cells usually demonstrated marked cloudy swelling. Moderate congestion was present, and iron stains frequently disclosed a fine deposit of iron in the portal areas.

The series of rabbits given 1 gm. of ferrous sulfate per kilogram of body weight and killed at intervals of one to thirty-five days constituted the most interesting group. Those killed during the first twenty-

four to forty-eight hours showed severe hemorrhagic periportal necrosis involving approximately a third of the substance of the liver lobules and containing a moderately heavy infiltration of polymorphonuclear leukocytes. Fat stains of liver sections from these animals indicated a moderate fatty vacuolization that was most noticeable in the periportal areas but was also present in the remainder of the liver lobules. Animals killed at the end of five and six days gave little evidence of necrosis. In these there was a slight degree of periportal proliferation of fibrous tissue and a slight infiltration of small mononuclear cells that were more evident in animals killed at the end of nine and ten days. Thereafter, there was but slight increase in the fibrous connective tissue of the portal areas. In most animals killed after two weeks the normal lobular architecture of the liver was distorted, with a fine diffuse hepatic fibrosis.

Discussion

The outstanding pathologic change in acute ferrous sulfate poisoning both in the human patients and in the laboratory animals studied was a hemorrhagic periportal necrosis. The areas damaged were so regular in distribution that the term "zonal necrosis" was truly applicable (Fig. 1). There are few conditions in which a truly zonal necrosis is found with regularity. Among these are usually mentioned the centrilobular necrosis of carbon tetrachloride and chloroform poisoning and the peripheral lobular necrosis of eclampsia and phosphorus poisoning. It is quite apparent that the cells in the peripheral portions of the hepatic lobules are more susceptible to damage by large amounts of iron than those in the central portion. This difference in susceptibility is presumably based on proximity of hepatic cells to the branches of portal veins bearing the absorbed iron to the liver. This raises the question of the possible danger of iron ingestion either in food or in therapy with large doses of iron in persons with poor hepatic function in cases of liver disease such as cirrhosis of the liver or in states of malnutrition with advanced fatty metamorphosis of the liver. In these situations of increased susceptibility of liver cells to toxic action it appears that iron may represent a significant toxic factor.

The healing and subsequent fibrosis of a severe periportal necrosis would quite readily, it is assumed, lead to a diffuse fibrosis, with breaking up of the normal pattern formation of a portal type of cirrhosis. It has not yet been proved that cirrhosis of the liver in man results from long-continued ingestion of iron though there are reports indicating that this is a possibility. Since the hepatic cells of the portal areas are more susceptible to toxic action of iron in the healthy person it can reasonably be inferred that in hepatic states, such as the marked fatty metamorphosis of malnutrition, moderate amounts of iron continually ingested may damage liver cells gradually and lead to a pigmentary type of cirrhosis such as that described in the African Bantu.[12]

Summary

Three fatal cases of accidental ingestion of medicinal ferrous sulfate preparations in children are presented. In all 3 cases and in rabbits the most important anatomic change produced by toxic doses was in the liver. Characteristically, hemorrhagic necrosis of the peripheral or periportal portions of the liver lobules was noted both in the patients and in the animals given appropriately large doses. These lesions appeared in rabbits receiving amounts of iron sufficiently great to cause death in approximately half the animals subjected to the dosage (1 gm. per kilogram of body weight). Larger amounts in nearly all animals caused death before sufficient time elapsed for the development of zonal necrosis and subsequent pathologic change. In the rabbit, survival of the administration of even one massive dose resulted in healing of the damaged periportal areas, with a diffuse hepatic fibrosis sufficiently pronounced to be termed a minimal cirrhosis.

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References

1. Forbes, G. Poisoning with preparation of iron, copper and manganese. *Brit. M. J.* 1:367-370, 1947.
2. Thomson, J. Two cases of ferrous sulphate poisoning. *Brit. M. J.* 1:640, 1947.
3. *Idem.* Ferrous sulphate poisoning: its incidence, symptomatology, treatment, and prevention. *Brit. M. J.* 1:645, 1950.
4. Spencer, I. O. B. Ferrous sulphate poisoning in children. *Brit. M. J.* 2:1112-1117, 1951.
5. Foucar, F. H., Gordon, B. S., and Kaye, S. Death following ingestion of ferrous sulfate. *Am. J. Clin. Path.* 18:971-973, 1948.
6. Smith, R. P., Jones, C. W., and Cochran, W. E. Ferrous sulphate toxicity: report of fatal case. *New Eng. J. Med.* 243:641-645, 1950.
7. Duffy, T. L., and Diehl, A. Ferrous sulfate poisoning: report of 3 cases. *J. Pediat.* 40:1-5, 1952.
8. Swift, S. C., Cefalu, V., and Rubell, E. B. Ferrous sulfate poisoning: report of fatal case. *J. Pediat.* 40:6-10, 1952.
9. Smith, J. P. Pathology of ferrous sulphate poisoning. *J. Path. & Bact.* 64:467-472, 1952.
10. Somers, G. F. Relative oral toxicity of some therapeutic iron preparations. *Brit. M. J.* 2:201-203, 1947.
11. Prain, J. H. Fatal poisoning of infant by anti-anaemic pills containing iron, manganese and copper. *Brit. M. J.* 2:1019, 1949.
12. Higginson, J., Gerritsen, T., and Walker, A. R. P. Siderosis in Bantu of southern Africa. *Am. J. Path.* 29:779-815, 1953.

REPLACEMENT OF SCAR WITH HAIR-BEARING SCALP*

EDGAR M. HOLMES, M.D.†

BOSTON

A PERSON with areas of absent hair attracts attention and is likely to become self-conscious and most anxious to have the deformity improved or, if possible, eliminated. If the area of absent hair is extensive such as that encountered when the entire scalp is lost, it is necessary to wear a wig or transformation to establish a hairy cover. If the patient is fortunate enough to have retained a large part of his hair, it is possible to transfer the hair-bearing scalp to the non-hair-bearing area in such a way that the defect becomes less conspicuous.

The skin of the scalp is quite resistant to stretching. This characteristic is due to the firm, tight aponeurosis to which the skin is firmly bound by fibrous bands. Once the nonstretching component is cut, the skin over it can be stretched appreciably. If parallel cuts are made, the overlying scalp may be stretched 3 or 4 mm. for each cut. In this manner a nonelastic scalp may be made to cover a fairly wide gap.

The blood supply of the scalp is abundant.[1] The many arteries coming in from all sides run parallel to the surface in the dermis and anastomose in a vascular plexus. The blood supply is so great that pedicles may be taken from many regions with impunity if the main arteries are incorporated in the flap. Sickle flaps and transverse flaps, theoretically, must be transferred with caution, but some may be used without previous delay.

Bipedicle flaps may be thin and long[2] without jeopardy to their blood supply. With such freedom in selection of flaps, laws followed in skin grafting in other parts of the body may be broken.

Defects on the top of the head offer a minor problem. They may be closed or diminished by several adjacent rotation flaps as described by Cushing,[3] Passot[4] and Tillman (as reported by Stone[5]) or by bipedicle flaps as suggested by Mitchell.[2] In some of these cases the central defect is reduced or eliminated at the expense of creating new, smaller defects at a distance that may be removed later. The scalp, like other skin, may be stretched by repeated partial excisions, and this principle is utilized whenever possible.

When the lost hair involves the hair margins, such as the front or side of the scalp, the problem is greater. Hair must be borrowed from above or behind the margin. Kazanjian[6] reported a case in which the entire front part of the scalp was covered with hair taken from the vertex and parietal region. This was accomplished by transposition of nonhair-bearing scalp with hair-bearing and skin grafting of any area that could not be covered. In this manner a bald area was covered with hair that, in turn, could cover by its length the denuded area created by the surgery.

The following case could have been treated in one of the ways mentioned above, but it did not appeal to me as much as the method described herewith.

CASE REPORT

D.G., a 19-year-old boy, received a burn of the right side of the head involving the scalp, ear and face. The helix of the ear was destroyed, and there was loss of hair-bearing scalp in a circle starting about 5 cm. above the helix and going in an arch backward to the occiput, ending in about the midline (Fig. 1*A* and *B*). This case presented two problems: the helix must be reconstructed, and the lost hair-bearing area restored.

The lost helix was reconstructed with the use of a clavicular rope graft, which was first transferred to the postauricular area and then spread out to cover the helix. Conchal cartilage was inserted to support the helix.

The nonhair-bearing scalp was nearly restored by means of 2 large, rotating flaps. The incision of the 1st flap was started just behind the forwardmost portion of the hair-bearing area where it joined the forehead and was carried in a large arch upward to the vertex and then down posteriorly toward the occiput, terminating just above the level of the helix (Fig. 2*A* and *D* and 3*A*). By rotation of this flap clockwise it was possible to bring the hair-bearing scalp down to the level of the crura of the helix, or the level to which one customarily shaves. This still left the area behind the ear and to the occiput only slightly reduced in size Fig. 2*B* and *E*). To cover this area as completely as possible, an incision was made from the lower limits of the hair-bearing scalp in the occiput in a large arc to the left halfway between the sagittal plane and the left ear upward, swinging around toward the midline but leaving a strip of at least 4 cm. of uncut scalp as some additional assurance of better blood supply. This permitted the flap to be rotated counterclockwise so that the inferior nuchal line on the affected side could be covered and all but 2 cm. of the burned area eliminated. When the incision was closed it was necessary to construct a "Z" to overcome a gaping defect between the flap and the intact scalp (Fig. 2*E* and *F* and 3*A*). At a later stage, the same flap could have been rotated once again, but the patient was satisfied with the result obtained and no further work was done (Fig. 3*B* and 4*A* and *B*). The patient wears his hair slightly longer than the average man to cover up the scars created by the incisions. His general appearance is considerably improved in that the conspicuous nonhair-bearing scalp has been largely eliminated and the auricular defect has been minimized.

SUMMARY

A case is reported to illustrate a method of replacing scar tissue involving the side of a head with hair-bearing scalp.

330 Dartmouth Street

REFERENCES

1. Conway, H., Stark, R. B., and Nieto-Cano, G. Arterial vascularization of pedicles. *Plast. & Reconstruct. Surg.* 12:348-363, 1953.
2. Mitchell, G. F. Total avulsion of scalp: new method of restoration. *Brit. M. J.* 1:13, 1933.
3. Cushing, H. W. Cranium. In Keen, W. W. *Surgery: Its principles and practice.* Vol. 3. Philadelphia: Saunders, 1912. Pp. 47-49.
4. Passot, R. *Chirurgie esthétique pure: techniques et résultats.* 300 pp. Paris: G. Danie, 1931.
5. Stone, J. S. Plastic surgery. In *American Practice of Surgery.* Edited by J. D. Bryant and Albert H. Buck. 1010 pp. New York: Wood, 1908. P. 630.
6. Kazanjian, V. H. Repair of partial losses of scalp. *Plast. & Reconstruct. Surg.* 12:325-334, 1953.

*From the Department of Plastic Surgery, Massachusetts Eye and Ear Infirmary.

†Instructor in otology, Harvard Medical School; assistant professor of otolaryngology, Boston University School of Medicine; chief of plastic surgery, Massachusetts Eye and Ear Infirmary; chief of otolaryngology, Newton-Wellesley Hospital.

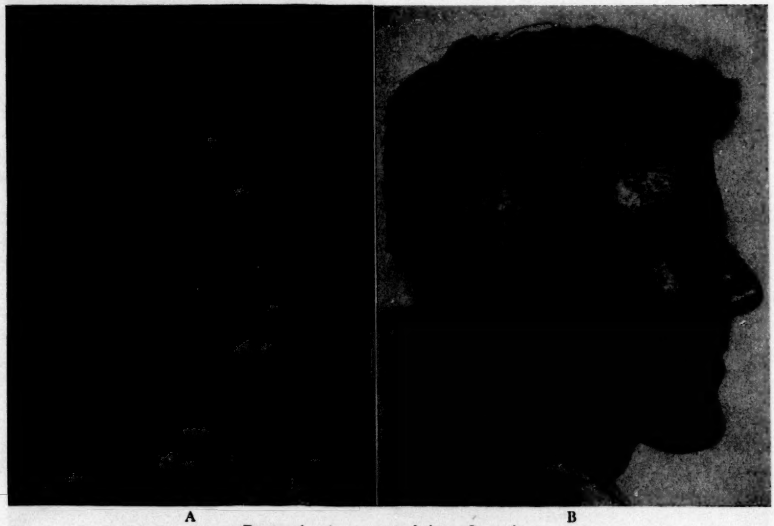


FIGURE 1. *Appearance before Operation. Note extent of absent hair and absent helix.*

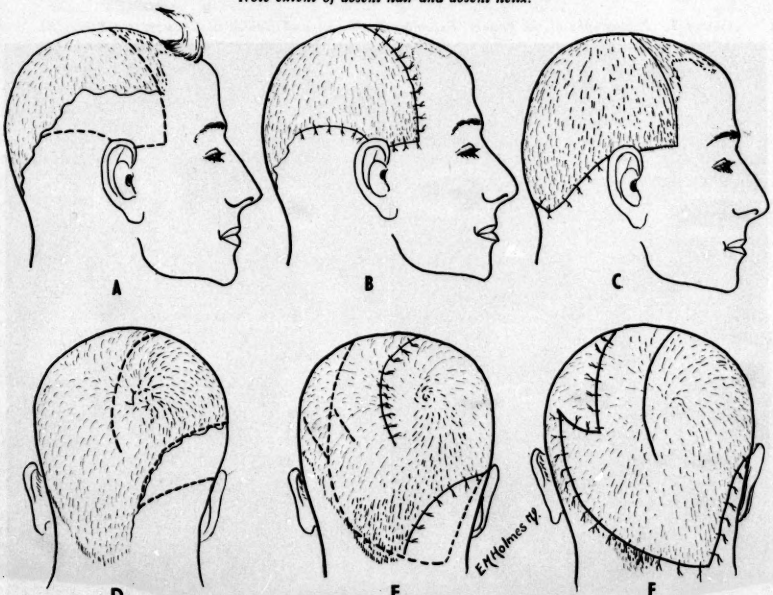
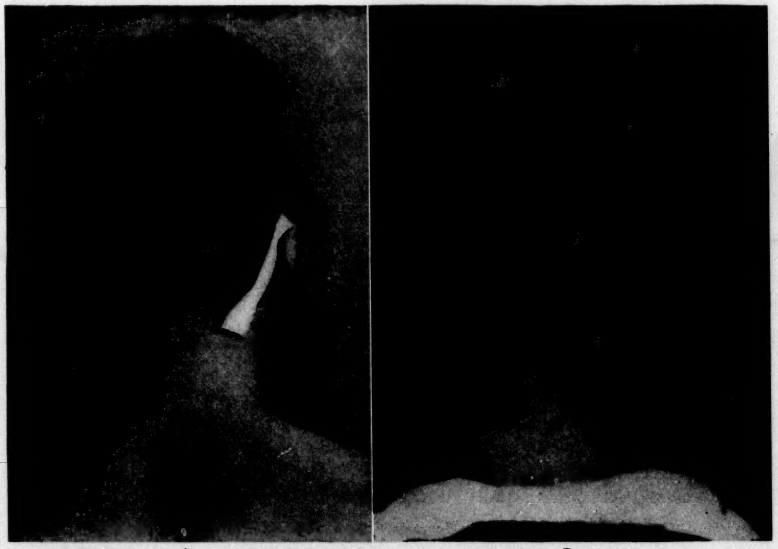
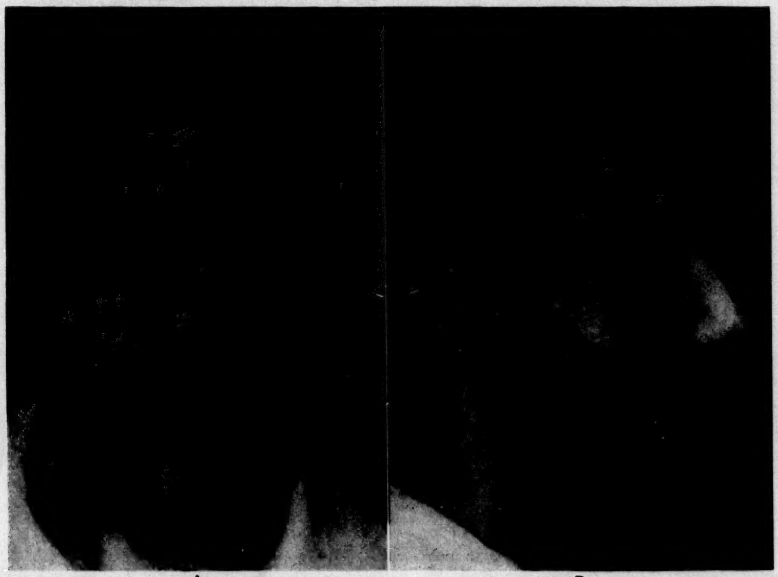


FIGURE 2. *Incisions Creating the First Flap, Which Was Rotated Clockwise to Cover the Area of the Temple (A and D), Second Flap, to Be Rotated Counterclockwise to Cover the Occipital and Postauricular Area (B and E) and Final Suturing and Resultant Scar Lines (C and F).*



A B

FIGURE 3. *Photographs of the Patient, Revealing Scars* (A) *and Hair Well Covering the Scars* (B).



A B

FIGURE 4. *Front* (A) *and Side* (B) *Views of End Result.*

JAUNDICE DURING CHLORPROMAZINE THERAPY*

JACOB ZATUCHNI, M.D., M.S. (MED.),† AND GLADYS MILLER, M.D.‡

PHILADELPHIA

CHLORPROMAZINE hydrochloride, 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride, is being used, apparently with remarkable benefit, in the treatment of various neuropsychiatric disorders and as an antiemetic, analgesic and sedative.[1-3] The following case is reported because of the occurrence of jaundice for which no cause besides chlorpromazine was found.

CASE REPORT

J.M., a 70-year-old woman, was admitted to the hospital on May 24, 1954, because of jaundice. For 3 years she had had many episodes of mental depression, for which electroshock therapy had been given on several occasions. Because the depressed state persisted she had entered a private mental institution, where, on April 28, administration of chlorpromazine had been begun in a dosage of 75 mg. daily, in 3 divided doses. On May 6, she was said to be increasingly agitated and confused. On the following day a temperature of 103°F. was noted, and penicillin was given, with subsequent defervescence in 24 hours. Meanwhile, chlorpromazine was continued without interruption. On May 11 jaundice appeared, the stools became clay colored, and biliuma was noted. The drug was stopped on that day. Laboratory studies showed an increase in the serum bilirubin that was due mainly to a rise in the promptly reactive type and negative flocculation tests (Table 1). The total protein was 6.5 gm., the albumin 3.7 gm., and the globulin 2.8 gm. per 100 cc.

Because the jaundice persisted the patient was referred to the Episcopal Hospital for additional studies and treatment. For several days before admission she had intermittent crampy midabdominal pain that was relieved by the passage of flatus or feces. She stated that her appetite was unimpaired, although she had a sensation of nausea. There was no pruritus. Her weight was usually 130 pounds but, during the past few months, had decreased to 103 pounds. Diabetes mellitus had been discovered 3 years previously during hospitalization for "nervousness," and 15 units of insulin had subsequently been taken each day.

Physical examination revealed a thin and jaundiced woman. The liver edge was felt 2 fingerbreadths below the right costal margin, with 13.5 cm. to the upper margin of dullness. The liver was not tender, and its edge was smooth. The stools were gray. Examination was otherwise negative. There was no fever.

On May 25 laboratory studies demonstrated considerable elevation of the serum bilirubin, almost entirely promptly reactive, and an increase in the alkaline phosphatase and total cholesterol (Table 1). The total protein was 6.0 gm., the albumin 4.3 gm., and the globulin 1.7 gm. per 100 cc.

TABLE 1. *Liver-Function Studies.*

DATE	BILIRUBIN			CEPHALIN FLOCCULATION	COLLOIDAL GOLD	THYMOL TURBIDITY		GAMMA-GLOBULIN TURBIDITY	INORGANIC PHOSPHORUS	ALKALINE PHOSPHATASE	CHOLESTEROL		
	PROMPT DIRECT	DELAYED DIRECT	TOTAL			VALUE	18-HR. RATIO				TOTAL	ESTERS	RATIO
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*			*units/100 cc.*	*%*	*units/100 cc.*	*mg./100 cc.*		*mg./100 cc.*	*mg./100 cc.*	*%*
May 12*	3.0	—	4.90	0	—	—	—	—	—	5.20§	250	170	68
May 25†	13.0	—	13.70	0	—	—	—	—	—	22.80¶	400	280	70
June 1‡	2.78	2.84	7.36	0	0	1.0	120	1.8	3.70	15.65¶	461	183	40
June 3‡	2.50	2.20	6.28	0	0	1.6	106	2.7	4.11	14.24¶	456	213	47
June 10‡	1.13	1.09	2.86	0	0	1.4	114	3.6	2.92	8.80¶	218	100	46
June 15‡	0.74	0.66	2.38	0	0	1.5	93	4.7	3.29	5.52¶	240	107	45
June 22‡	0.56	0.50	1.70	0	0	1.0	120	4.6	3.26	4.46¶	282	134	48
June 29‡	0.08	0.07	0.37	0	0	1.1	118	4.5	3.51	4.99¶	294	158	54
Normal value‡	0-0.2†	—	0.25-0.85	0-+	0	0.3	85-100+	3-8	3-4.5	2-9	110-180	—	50-75

*Data from Dr. E. Downs Longaker, Medical Department, Smith, Kline & French Laboratories, Philadelphia.
†Data from Episcopal Hospital.
‡Data from Samuel S. Fels Research Institute, Temple University School of Medicine.
§Bodansky units.
¶Shinowara-Jones-Reinhart units.

Examination of the blood showed a red-cell count of 4,090,000 and a white-cell count of 7200, with 75 per cent neutrophils and 25 per cent lymphocytes. The hematocrit was 43 per cent, and the erythrocyte sedimentation rate (Wintrobe method) was 30 mm. per hour. Urinalysis revealed the presence of bile and a trace of protein. There was no occult blood in the feces. The prothrombin time was calculated on several occasions and was never lower than 85 per cent. An electrocardiogram was normal. Roentgenographic study of the chest and barium-enema examination of the gastrointestinal tract were negative.

On May 28 an exploratory laparotomy was done. The pancreas, gall bladder and liver appeared normal. No obstructive lesion was identified. Biopsy of the liver was obtained. A T tube was inserted into the common bile duct, and the abdomen was closed.

Convalescence was uneventful. Diabetes was easily controlled by diet and 20 to 26 units of NPH insulin daily. Later, there was a gradual decrease in the requirement for insulin, which was finally discontinued on June 25.

Microscopical study of the liver sections showed preser-

*From the departments of Medicine, Temple University School of Medicine and Hospital, and Episcopal Hospital.
†Associate in medicine, Temple University School of Medicine and Hospital, and Episcopal Hospital.
‡Resident in internal medicine, Temple University School of Medicine and Hospital.

vation of the basic architecture (Fig. 1). The portal area was infiltrated by neutrophils, eosinophils, lymphocytes and mononuclear cells, which extended into the adjacent hepatic parenchyma (Fig. 2). The biliary radicles were not dilated and demonstrated no proliferative change. A few canaliculi were plugged with bile. Some periportal hepatic cells were

FIGURE 1. *Acute Inflammatory Reaction in the Portal Area (X90).*
The basic architecture of the liver is unaltered.

degenerated and others were the seat of phagocytosis (Fig. 3). The findings were interpreted as consistent with an acute cholangiohepatitis.

Studies of liver function were done repeatedly (Table 1).

The T tube was removed on June 8, after a cholangiogram had confirmed the absence of any extrahepatic obstruction. The stools became brown on June 17, and clinical jaundice disappeared on June 19.

On June 22 another liver biopsy (intercostal approach) revealed a distinct lessening of the inflammatory reaction. The hepatic cells appeared normal, and there was minimal cellular infiltration of the portal area (Fig. 4). Bromsulfalein tests (5 mg. per kilogram of body weight) on June 23 and June 29 disclosed 2.5 per cent retention of the dye at the end of 45 minutes.

On June 30 the patient was discharged from the hospital. She was asymptomatic, and clinical examination was negative.

DISCUSSION

Because of the history of mental symptoms, abdominal pain and considerable weight loss in an elderly woman with apparently controlled diabetes carcinoma of the pancreas was seriously considered as the cause of the obstructive jaundice. For this reason, an exploratory laparotomy was performed, revealing neither carcinoma nor, indeed, any obstructive lesion of the biliary tract.

We were therefore certain that we were dealing with an intrahepatic obstructive jaundice, and this was supported by the normal cholangiogram. Interestingly enough, the presence of an intrahepatic obstructive lesion was originally suggested by the ratio of the alkaline phosphatase (Shinowara—Jones—Reinhart units) to the total cholesterol (in hundreds). A value of 7.5 units or less, which was always present in our patient, is commonly found in intrahepatic and rarely in extrahepatic obstructive jaundice.[4]

An inflammatory hepatitis was considered unlikely as the cause of the lesion in view of the sudden onset of jaundice without prodromal symptoms, anorexia or

FIGURE 2. *Infiltration of the Portal Area by Neutrophils, Eosinophils, Lymphocytes and Mononuclear Cells Extending into the Adjacent Hepatic Parenchyma (X300).*

fever. The total and differential leukocyte counts were normal. There was no lymphocytosis. The urine showed no increase in formed elements. Finally, an inflammatory hepatitis is rare with negative flocculation tests.

The occurrence of jaundice during chlorpromazine therapy has been observed by others.[1,5] At present it is thought to be rare. Indeed, to our knowledge, only 6 cases have been reported in the literature. Lehmann and Hanrahan[1] noted jaundice of less than ten days' duration in 3 patients who had received the drug for two, three and four weeks respectively, and Winkleman[5] mentioned the occurrence of jaundice in 3 persons two to five weeks after the administration of the drug. In our patient clinical jaundice appeared on

the fourteenth day of chlorpromazine therapy and was present for forty days.

Although many chemicals may produce necrosis of the liver, the changes observed in our patient simulated those seen in hepatitis induced by arsphenamine,[6] thiouracil[7] and methyltestosterone.[8] Essentially, there appears to be a primary injury of the small biliary passages, which are plugged with bile and surrounded by myriads of cells that are predominantly mononuclear but with varying numbers of polymorphonuclear forms, including eosinophils. The seat of the reaction is in the portal area.

The mechanism of these changes is unknown. With other chemically induced hepatitides various hypotheses have been advanced, such as direct injury, change in bile viscosity, sensitization and the removal from the liver of some essential metabolite.[6-8] Because of the increased sedative effect of chlorpromazine in patients with liver disease, Moyer et al.[9] suggest that the drug may be transformed in the liver.

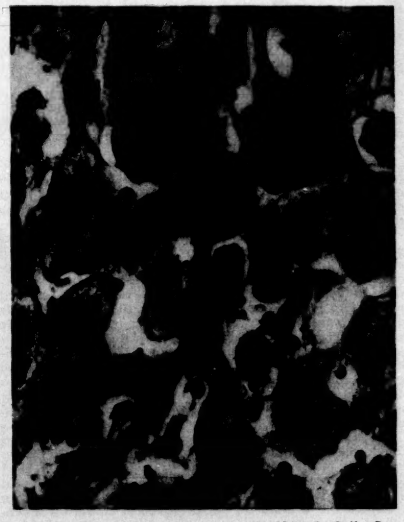


FIGURE 3. *Degenerative Changes in the Hepatic Cells, Some of Which Are Being Phagocytosed (X800). Bile thrombi are seen in the canaliculi.*

Hypersensitivity may be the principal mechanism, even though chlorpromazine has antihistaminic properties and a chemical structure similar to that of some antihistaminic compounds.[3] Indeed, the frequency of urticaria and asthma was 13 per cent in the experience of Lehmann and Hanrahan.[1] Although our patient had no peripheral eosinophilia the liver biopsy showed many eosinophils in the cellular infiltrate. Moreover, the sudden appearance of fever on the ninth day of chlorpromazine therapy may have been drug induced. In our limited experience with this drug we have seen 1 other patient in whom fever occurred on the fourth day of chlorpromazine therapy and was accompanied by great weakness and drowsiness. Cessation of the drug was followed by prompt defervescence and disappearance of symptoms.

So far, jaundice has appeared only during chlorpromazine therapy. However, it is important to be aware of experiences with other chemically induced hepatitides that became clinically apparent not only during administration of the drug but also, in some cases, at a variable period after its withdrawal.

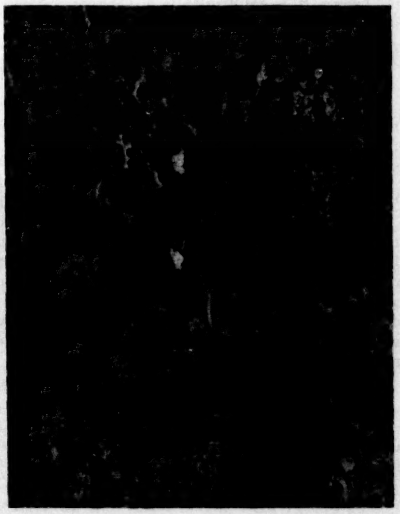


FIGURE 4. *Liver Biopsy after Jaundice Had Subsided (X500).*

The inflammatory reaction has almost completely disappeared, and only minimal evidence of bile retention is seen. Note the foreign-body giant cell, with lipid vacuolization, in the center of the field.

SUMMARY AND CONCLUSIONS

Chlorpromazine may have a hepatotoxic effect that becomes clinically manifest as an obstructive jaundice. A case in which jaundice appeared on the fourteenth day of chlorpromazine therapy and persisted for forty days is reported. Laboratory studies showed hyperbilirubinemia, principally of the promptly reactive type, elevated alkaline phosphatase, slightly increased total cholesterol and negative flocculation tests. Liver biopsy revealed cellular infiltration of the portal area and minimal parenchymal involvement. Convalescence was uneventful, and another

liver biopsy, after clinical jaundice had subsided, demonstrated almost complete clearing of the exudative reaction. Reasons are given for the suggestion of drug hypersensitivity as a possible cause of these effects.

We are indebted to Dr. Charles Harris, pathologist, Fels Research Institute, Temple University School of Medicine, who prepared the illustrations.

References

1. Lehmann, H. E., and Hanrahan, G. E. Chlorpromazine: new inhibiting agent for psychomotor excitement and manic states. *Arch. Neurol. & Psychiat.* **71**:227-237, 1954.
2. Friend, D. G., and Cummins, J. F. New antiemetic drug: preliminary report. *J.A.M.A.* **153**:480, 1953.
3. Sadove, M. S., Levin, M. J., Rose, R. F., Schwartz, L., and Witt, F. W. Chlorpromazine and narcotics in management of pain of malignant lesions. *J.A.M.A.* **155**:626-628, 1954.
4. Shay, H. Personal communication.
5. Winkleman, N. W., Jr. Chlorpromazine in treatment of neuropsychiatric disorders. *J.A.M.A.* **155**:18-21, 1954.
6. Hanger, F. M., Jr., and Gutman, A. B. Postarsphenamine jaundice: apparently due to obstruction of intrahepatic biliary tract. *J.A.M.A.* **115**:263-271, 1940.
7. Gargill, S. L., and Lesses, M. F. Toxic reactions to thiouracil: report of cases with one fatality. *J.A.M.A.* **127**:890-898, 1945.
8. Werner, S. C., Hanger, F. M., and Kritzler, R. A. Jaundice during methyl testosterone therapy. *Am. J. Med.* **8**:325-331, 1950.
9. Moyer, J. H., et al. Laboratory and clinical observations on chlorpromazine (SKF-2601-A) — hemodynamic and toxicological studies. *Am. J. M. Sc.* **227**:283-290, 1954.

MENTAL DEPRESSION IN HYPERTENSIVE PATIENTS TREATED FOR LONG PERIODS WITH LARGE DOSES OF RESERPINE*

EDWARD D. FREIS, M.D.†

WASHINGTON, D. C.

THE introduction of *Rauwolfia serpentina* into this country by Wilkins and Judson[1] and the purification of an active alkaloid, reserpine (Serpasil), has led to the widespread clinical use of the latter drug not only in hypertension[2,3] but also in neuropsychiatric conditions.[4] The purpose of this report is to describe the development of psychiatric complications in hypertensive patients treated with large doses of reserpine for long periods.

Case Reports

CASE 1. Mrs. I.K., a 54-year-old widow, had mild hypertension for 1 year associated with headache and substernal pain. Since the death of her husband 2 years previously she had been more emotional and easily upset than formerly. The blood pressure was 190/105. The fundi showed Grade 1 changes; the heart was normal in size, and examination of the urine was negative.

The patient was treated with reserpine, 0.5 mg. twice daily, and alkavervir (Veriloid), 4 mg. 3 times daily, the average blood pressure falling to 165/100. There was no change in symptomatology until 4 months after treatment was instituted, when, after a vacation trip to visit her mother, she began to feel extremely depressed. She was conscious of "everything in her body" and was worried about her blood pressure. She did not believe that life was worth living. She wanted to remain at home and was incapable of enjoying any of the pursuits that had formerly given her pleasure.

Reserpine and alkavervir were withdrawn, and phenobarbital, 60 mg. 4 times daily, was substituted. She improved slowly for the succeeding 2 months and had remained free of depression when last seen six months later.

CASE 2. Severe hypertension developed in W.H., a 44-year-old college professor, over a period of 3 years. When he was first seen in 1950 the blood pressure was 240/140, the fundi showed Grade 3 changes, with hemorrhages and exudates, and the heart was greatly enlarged; the urine gave a ++ test for albumin.

He was treated with alkavervir for 6 months, and then parenteral administration of hexamethonium was substituted. There was remarkable improvement, with reduction of average blood pressure to 160/100, regression of changes in the optic fundi to Grade 1, decrease in the heart size and clearing of the albuminuria. He returned to a full-time schedule of teaching, feeling better than at any time in the past 5 years.

In September, 1953, the treatment was changed to pentolinium tartrate (pentapyrrolidinium, or M&B 2050), 100 mg. orally 3 times daily, and reserpine, 0.5 mg. 3 times daily. Sleepiness and lethargy developed so that after 2 weeks the dosage was reduced to 0.5 mg. twice daily.

The patient continued to feel extremely well until January, 1954, when he became severely depressed. He lost all self-confidence and became fearful of meeting people socially, including his close friends, and excessively introspective and lost all enthusiasm for his work. He debated whether to escape into alcoholism but did not do so. He did not want to leave his room or to meet anyone. He wished for death but did not contemplate suicide.

He did not manifest anxiety so much as inertia of intellect and loss of capacity to enjoy life. His appetite remained good during this period, and he gained weight despite his depressed outlook. His ability to concentrate was markedly retarded in that he fumbled for words during lectures and was unable to digest the current literature in his field.

He lived in another city and did not communicate his intellectual and emotional change to this clinic. Nevertheless, there was a slight improvement in the spring of 1954 despite the fact that he continued to take reserpine. In June, when he was readmitted to the hospital for a checkup, reserpine was withdrawn, but pentolinium tartrate was continued. He began to improve dramatically after 48 hours and within a week was restored to his usual mental and emotional vigor.

CASE 3. Mrs. R.K., a 41-year-old housewife, had hypertension of 5 years' duration. The blood pressure was 220/135, and the fundi showed Grade 3 changes, with hemorrhages but no exudates. Cardiac and renal findings were not significantly abnormal. She was hospitalized and treated with alkavervir, 4 mg. 3 times daily, and reserpine, 0.5 mg. twice daily. After 1 week the dosage of reserpine was reduced to 0.25 mg. once daily.

After discharge from the hospital the home recordings of blood pressure averaged 150/100. The patient felt well until 4 months after treatment was instituted, when she became "chronically unhappy" and "nothing pleased her" and yet she could find no external reason for her dissatisfaction. Whereas previously she had always been extremely active and enjoyed shopping tours and club visits with her friends, she did not want to leave the house and did not

*From the Cardiovascular Research Laboratory, Georgetown University Hospital, the Department of Medicine, Georgetown University School of Medicine, and the Veterans Administration Hospital.

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†Adjunct clinical professor of medicine, Georgetown University School of Medicine; chief, Medical Service, Veterans Administration Hospital; chief, Cardiovascular Research Laboratory, Georgetown University Hospital.

enjoy her friends. Ordinary household duties were accomplished with great effort. There was no loss of appetite and little anxiety associated with this depression. The dosage of reserpine was reduced to 0.1 mg. a day for 2 weeks, but the symptoms persisted. Reserpine, but not alkavervir, was then discontinued, and within 1 week she returned to her previously happy emotional and vigorous physical state.

CASE 4.* J.J., a 60-year-old executive, had had hypertension for 10 years. In the past year the blood pressure had been about 200/120, but he had no hypertensive symptoms. He always had been rather tense and anxious and suffered from a moderate degree of claustrophobia. The fundi showed Grade 1 changes; the heart was not enlarged, and urinalysis was negative. The office recording of blood pressure was 210/115, but several recordings at home averaged 180/105.

He was treated with an extract of *Rauwolfia* (Rauwiloid), 4 mg. twice daily for 1 month, and since there was no change in blood pressure alkavervir, 5 mg. twice daily, and reserpine, 0.5 mg. twice daily, were substituted. On this regimen the blood pressure at home varied between 140/90 and 180/100. Because of continued feeling of emotional tension the dosage of reserpine was increased to 1.0 mg. twice daily after 1 month. The patient felt calmer and was quite well for the ensuing 2 months, when, immediately after his daughter's marriage, an acute depression with agitation developed. He was afraid to leave the house without his wife. His claustrophobia became so severe that he would not step into an elevator. He thought that he had become a burden to everyone and lay awake at night contemplating suicide.

Reserpine, but not alkavervir, was discontinued, but because of the severity of the symptoms the consulting psychiatrist decided to give him electroshock therapy without delay. After a short course of treatment the patient began to improve slowly and was soon back at work.

CASE 5. H.B., a 52-year-old retired policeman, first had malignant hypertension in 1950. When he was seen in the hospital in 1950 the blood pressure was 230/140, the fundi showed Grade 4 changes, and the heart was enlarged, with pulmonary congestion; there was impairment of renal function without nitrogen retention.

He responded well to treatment with hexamethonium subcutaneously and 1-hydrazinophthalazine (Apresoline) orally and remained on that regimen until May, 1953, when pentolinium tartrate by mouth was substituted for the subcutaneous administration of hexamethonium. At this time reserpine, 0.25 mg. 3 times daily, was also given, this regimen being continued for approximately 1 year, during which the average blood pressure was 165/95. He felt quite well.

On April 4, 1954, because of the development of easy fatigability and lassitude, the dosage of reserpine was reduced to 0.25 mg. once daily. Nevertheless, he continued to feel tired and also became depressed. He did not wish to leave the house, but at home he did not enjoy television, working in the garden or any of the other pursuits in which he had formerly taken pleasure. He woke up in the early hours of the morning and during this time considered various methods of committing suicide. Whereas he had previously been affably aggressive and talkative he now appeared quiet, uncertain and depressed. Reserpine was discontinued, and he was followed by a psychiatrist. He improved slowly for several weeks but, when last seen, had still not returned completely to his previous personality state.

DISCUSSION

Although several drugs were used in these cases the evidence as a whole strongly suggests that the emotional disorders reported were brought on by reserpine. Reserpine was the only agent used in all the patients, some receiving veratrum alkaloids and others pentolinium bitartrate with or without 1-hydrazinophthalazine. Furthermore, no psychiatric complications of the kind described in these case reports were observed in patients taking any of the other antihypertensive agents without reserpine. Finally, in 4 cases the depression cleared after reserpine had been discontinued. Thus, it appears that reserpine rather than any of the other drugs was the most important contributing factor in the development of the depressed state.

The emotional reaction of several patients did not appear to be that of a true anxiety depression. They manifested withdrawal from the environment, lethargy and unhappiness but not anxiety. In addition, anorexia and weight loss did not occur. Nevertheless, all considered life not worth living, and 2 of them contemplated suicide.

Lesser degrees of depression have frequently been encountered in other patients in this clinic. Common symptoms, often so mild as to pass without comment unless specifically asked for, were lack of ambition, crying spells, introspection and lethargy.

It is worthy of note that the dosage of reserpine in all cases except 1 was maintained at a higher level than that advised customarily, being 1.0 mg. a day in 2 and 1.5 and 2.0 mg. a day, respectively, in 2, only 1 of the patients being maintained on a dose of 0.25 mg. a day. It is also noteworthy that in every case the drug had been administered continuously for two months or longer before the symptoms of mental depression appeared. In 1 case the appearance of the syndrome was delayed for approximately a year after the institution of treatment. Once depression developed, however, reduction of the daily dosage from 0.25 to 0.1 mg. (Case 3) and from 1.0 mg. to 0.25 (Case 5) failed to relieve the symptoms, and complete withdrawal of the drug was necessary.

It is also apparent that disturbing environmental factors may have played a part in the development of the syndrome. In Case 1 depression developed after the patient visited her mother, and in Case 4 it followed the marriage of the patient's daughter. In the remaining cases, however, no obvious precipitating factors were evident.

Since reserpine is being used widely at present for the treatment of mental illness, as well as hypertension, it seems appropriate to call these cases to the attention of the medical profession, so that accumulated experience can confirm or reject the implication of this report that reserpine caused the psychiatric condition described. Although similar psychiatric complications were not observed in patients treated with other *Rauwolfia* preparations it must be emphasized that the great majority of the patients in this clinic were treated with reserpine rather than with other extracts. Therefore, the experience with other drugs containing *Rauwolfia* is too limited for one to pass judgment on whether they are also apt to produce this syndrome.

*We are indebted to Dr. Robert Nenno, assistant chief of the Department of Psychiatry, Georgetown University Hospital, for diagnosis and treatment of the psychiatric complications that developed in this and the subsequent case.

Summary and Conclusions

Five cases of mental depression are described. These developed in hypertensive patients after several months of continued treatment with reserpine in dosage varying from 1.0 to 2.0 mg. a day in 4 and 0.25 mg. a day in 1 of the cases. Maintenance doses of this agent should be kept as low as possible, preferably below 0.25 mg. a day, to minimize the development of this syndrome.

References

1. Wilkins, R. W., and Judson, W. E. Use of *Rauwolfia serpentina* in hypertensive patients. *New Eng. J. Med.* **248**:48-53, 1953.
2. Wilkins, R. W., et al. Reserpine in treatment of hypertension: note on relative dosage and effects. *New Eng. J. Med.* **250**:477, 1954.
3. Freis, E. D., and Ari, R. Clinical and experimental effects of reserpine in patients with essential hypertension. *Ann. New York Acad. Sc.* **59**:45-53, 1954.
4. Kline, N. S. Use of *Rauwolfia serpentina* Benth. in neuropsychiatric conditions. *Ann. New York Acad. Sc.* **59**:107-132, 1954.

SPECIAL ARTICLE

QT BOSTON — AN ILEOSTOMY GROUP

Edith Lenneberg*

Newton, Massachusetts

In the field of patient rehabilitation an increasingly greater role is played each year by lay organizations. Conditions that require constant care by the patient himself or are socially embarrassing have given particular impetus to mutual-aid societies for "qualified" members only — for instance, the American Diabetes Association and Alcoholics Anonymous. Organized self-help has in some cases become an important tool at the disposal of the physician in teaching his patient to live with a handicap.

History

Unaware of this trend, 9 young women with ileostomies met for the first time in Boston in October, 1952. The objective was to talk over informally some of the difficulties encountered in the practical management of an ileostomy. Shortly after this successful get-together, the attention of the group was called to a letter describing the activities of an ileostomy club in New York, the QT Alumni of Mount Sinai Hospital.† Contact was established, and the name, although referring to the Q and T wards at the Mount Sinai Hospital (aside from the slang significance of keeping things quiet), was adopted by the Boston group for the sake of unity. QT alumni's cooperation and the mere fact of its existence were encouraging factors in the growth of the Boston organization.

Soon it became apparent that QT of Boston was here to stay. Monthly meetings were instituted; membership grew rapidly, with new members present at every meeting to date. The mailing list, which includes all New England, contained 48 people with ileostomies at the end of the first season and 95 at the end of the second.

Meetings

The first five meetings were restricted to women. Only young women had been asked for the sake of congeniality, which, it was believed, would reduce embarrassment. Inadvertently, an older woman was invited, and her presence proved to be an asset; without further discussion, membership was opened to any woman with an ileostomy. The question of male participation arose repeatedly, and it was decided to invite a number of men and to discuss with them the possibility of their joining. Ten men came in response to the invitation. Their enthusiasm was great, and nothing would persuade them that they might prefer to meet among themselves. A unanimous vote incorporated them into the group. Since then membership has been open to anyone with an ileostomy. The heterogeneous element has actually been helpful in creating a realistic life situation and has given many members their first opportunity to discuss the ileostomy with someone of the opposite sex.

Meetings, which are held on the first Sunday afternoon of each month, are alternately closed and open to interested outsiders. Closed sessions serve two purposes: to discuss private details and to settle organizational matters. Open meetings are more formally instructive; a professional person is invited as a speaker, and a question period follows his talk. It is on such occasions only — when the speaker is a physician — that medical questions are permitted; at closed sessions medical questions are referred to the inquirer's physician. Originally, there was much talk of operations, symptoms, drugs and medications. Once the cathartic effect had taken place for the group as a whole, this type of conversation subsided and became the stamp of the newcomer. A code of ethics, which has been established by silent agreement, permits him to voice these traumatic experiences, but the lack of curiosity that greets his comments soon convinces him that his experiences are not unique.

Emotional Impact

Newcomers to the group, whether with a new ileostomy or with one of long standing, often express

*Chairman, QT Boston.

†Lyons, A. S. Ileostomy club. *J.A.M.A.* **150**:812, 1952.

astonishment at seeing "so many people with an ileostomy." "My doctor told me," they say, "but I didn't really believe it." Nothing can replace the psychologic impact of meeting a large group of peers who look healthy and normal and who — most of all — know the significance of small problems which loom so large to the lonely person. Whereas the doctor, the nurse and the social worker are understanding, the peer understands. Even if he never returns to a meeting, the new member comes away with an altered perspective and, frequently, renewed determination to see his problems through.

The meetings close in time to permit informal conversation over refreshments, which adds a club-like touch, encouraging personal contact between members.

Technical Information

There is a display each time of all appliances on the market. Veteran patients who often have never heard of an appliance besides the one they are using and, in fact, often are not aware that their appliance is unsatisfactory, as well as neophytes, find it helpful to see these bags before they make a choice. Advice on nearly every one can be given on the premises by someone with personal experience. This is an invaluable aid in selection, for many a patient finds himself without any criteria by which to evaluate an appliance and to judge which one might be suitable for him. Having learned something about them, he can discuss his choice intelligently with his physician. Recently, a collection of temporary appliances and home-made appliances for special individual problems has been initiated.

Cements and adhesives are a frequent topic of conversation, as are deodorants and cleansing methods; other technicalities discussed concern changing of the appliance, including frequency, manners of wearing the belt, flushing of the appliance while it is being worn, methods of closure, night-time problems, use of a girdle, clothing and innumerable small tricks that help to reduce the nuisance of caring for an ileostomy.

Practical Problems

It came almost as a surprise to the first members of QT to discover that the more problems they solved, the more they could see, until it became quite clear that one could not have an ileostomy and not be reminded of it in everything one did. Every activity when undertaken for the first time requires that thought be given to the ileostomy in this particular situation. Time and again, "coping" became, and still is, a topic for discussion. The gamut runs from sports and traveling, through school, jobs, military service and insurance problems, to personal relations, pregnancy and adoption. Accordingly, one meeting was devoted to the family's adjustment to the patient's ileostomy, and members of families were specifically invited to attend that meeting. Another meeting featured a members' panel on how to tell their children about their ileostomies.

Since most members wish to hide the fact that they have an ileostomy, these social problems represent in many cases a formidable obstacle to good adjustment. Although some of them can be eliminated through the acquisition of technical information, others require specific evaluation, something that can well be accomplished by a group of peers. Letting the hair down has been a long-hoped-for relief to many members who never had met anyone with an ileostomy and for years smarted under the knowledge of their secret. Once the first painful words have been spoken a willingness to divulge to outsiders the existence of the ileostomy often follows, and thus the particular social problem is resolved.

In situations in which facts must be collected — as in certain employment difficulties or insurance questions — it is the responsibility of the officers of the organization to provide such information.

Border-Line Problems

Probably, the most frequent difficulty plaguing these patients is skin trouble. With the exception of inability to tolerate a certain kind of cement or adhesive, this difficulty is due to improper fit or adhesion of the appliance disk. To find an appliance that fulfills the patient's requirements and, moreover, remains effective at all times appears to be exceedingly difficult. Certainly, no one appliance existing today is satisfactory for all patients; body contour and site and size of ileostomy vary too greatly. But, even after an apparently good appliance has been found and well fitted, problems of inexplicable origin arise from time to time, and each problem announces itself in the form of skin trouble, whether it is merely itching and redness or papules and even breaking down of tissue and weeping. Once the skin is moist, no appliance will adhere; ileal discharge will touch the skin and break it down further.

It is inevitable that patients so universally troubled should try their best to help their doctors solve the problem. The first members of QT were well aware of the inter-relation here between the technical and the medical, and agreed to the following rule: all information about products that come in direct contact with the skin must be submitted to the patient's personal physician before trial, except cements that can be tested by means of a patch, as described below. The rule has been extended to cover all borderline problems. To my knowledge there has been no transgression.

Services

Visiting

From the outset members who had been operated on years ago commented on the existence of a group such as this in the following way: "If only I could

have talked to someone with an ileostomy when I first had mine!" Memory of the early months — often years — of unhappiness and ignorance has been the prime mover in the adoption of a program of assistance to new and prospective ileostomy patients. Foremost here is visiting. There is hardly a QT member who has not at one time or another expressed his desire to visit a new patient. For those who have done it, one astonishing result has been the feeling of self-help alongside the altruistic pleasure of helping another. For those who have received the visits, the feeling of helplessness — both emotional and practical — has been greatly reduced.

Owing to the independent status that QT has consistently maintained to be of service to all patients, doctors and hospitals who might require them, a flexible procedure has been worked out for the implementation of visiting services. A visiting chairman has been appointed through whom all visits are channeled. Calls are received from doctors, social workers and hospital wards, describing the patient and his situation. A member is then chosen by the chairman with a view to matching effectively sex, age, marital status, geographic location, appliance used, personal background and other details of compatibility. In the absence of a good match, the chairman herself will go. Close contact with the referring professional worker is maintained until the new patient is comparatively rehabilitated and able to attend meetings.

QT hopes that the day will come when every new ileostomy patient will automatically receive a visit, and when every prospective patient will have an opportunity to make his decision on the basis of having seen with his own eyes that QT members are normal and active people.

Cement Kits

From time to time a problem arises that requires a large effort. This becomes a special project, and responsibility is given to a member who expresses interest in it. A good example is the cement patch-test kits, which have been added this year to the services offered by QT Boston.

To detect intolerance of a certain kind of cement and thereby to reduce the risk of skin trouble, it has been found advisable to give a patch test to each cement on an area with skin similar to abdominal skin before use with an appliance. A kit has been made up containing at present 7 different types of cement and 7 rubber patches, as well as a set of directions. The kit is available free of charge.

Samples

New products of all kinds continually come to the attention of the group. Some, specifically designed for the needs of ileostomy patients, are sent by manufacturers. Others may be mentioned as having a possible application. All such products are distributed as samples to members at meetings; each member is required to submit a written report on his evaluation. Of course, this arrangement does not include ileostomy appliances.

Bulletin

Information is a vital part of rehabilitation. The new patient, the patient who has struggled for years with a certain problem, the patient who lives in a small town where no one else has an ileostomy and the patient who cannot attend meetings all need information and education on the facts about an ileostomy. A monthly bulletin goes out to them containing résumés of talks given at meetings, brief outlines explaining in simple language the physiology of the digestive system, price lists of certain products, helpful hints of all kinds, personal news representing achievement for a patient with an ileostomy and news of other ileostomy groups — in short, any information that might aid members. The bulletin is doubling at present as an educational medium and a publicity sheet. Besides going to ileostomy patients it is being sent to a rapidly growing group of New England doctors (115 at this writing), who have expressed interest in QT's work.* Manufacturers, too, are on the mailing list, and plans are under way to include in the near future medical social workers and nurses. To publicize the existence of QT among professional and semiprofessional workers seems to be an important step, for to them QT represents a significant aid in rehabilitating some of their most dependent patients. The ileostomy patient is restored to health only when he has worked out his practical and technical problems so completely that he can *afford* to forget about the ileostomy.

Information Pool

QT considers the persistent pooling of information the best approach to the solution of its nonmedical problems. Officers and working members are carefully recording all data on nonmedical topics relevant to ileostomy. A file is growing steadily; another year should make it possible for the group to present these data in easily accessible and amendable form to all ileostomy patients as well as professional people interested in the problems concerned.

Co-operation is sought not only from members, physicians and manufacturers but also from other ileostomy groups that are growing up in various parts of the country. Besides the Mount Sinai organization mentioned above, a club is in existence in New York at the Bronx Veterans Administration Hospital. Philadelphia has a group that includes colostomy patients. In Los Angeles a new group has been started this year. Several inquiries have been received from smaller New England cities where enough people have ileostomies to warrant the formation of a club.

*Anyone who wishes to be placed on the mailing list or to obtain information should communicate with QT's secretary, Mrs. Sylvia Kirshen, 73 Newport Street, Arlington, Massachusetts (telephone: ARlington 5-5567-J).

Summary and Conclusions

A lay organization that serves ileostomy patients in the New England area by means of monthly meetings, visiting services, a bulletin and a pooling and exchange of practical and technical information is described. Emotional benefits are derived from the companionship with peers. This group helps the physician return his ileostomy patient to independence and normal, active living.

MEDICAL PROGRESS

BIOCHEMISTRY OF HUMAN CANCER (Concluded)*

Henry M. Lemon, M.D.,† Burnham S. Walker, M.D., Ph.D.,‡
M. Moira Davison Reynolds, Ph.D.,§ and Herbert H. Wotiz, Ph.D.¶

BOSTON

Alteration of Urinary Constituents

Steroids. The relation of urinary steroids to neoplastic disease was first systematically explored by Dobriner,[242,243] whose investigations stimulated many other laboratories to engage in the problem and to improve the methods of assay. The stereospecificity of urinary adrenal steroid metabolites was a matter of debate until Dorfman and his colleagues[244] obtained stereochemical correlation of isomers at the 3-carbon and 5-carbon positions. This may provide an insight into the nature of enzymes involved in steroid metabolism and contributes to better chemical procedures differentiating urinary metabolites arising from adrenal cancer and those originating from adrenal hyperplasia. The application of urinary 17-ketosteroid analysis to this and other problems has been well reviewed elsewhere.[245] Patients with cancer frequently show a nonspecific decline in urinary 17-ketosteroids.

A specific steroid excretion pattern has not yet been established in the urine of patients with cancers, except for some of those with tumors primary in the adrenal cortex or gonads. Differentiation of the etiology of virilizing syndromes, usually associated with elevated 17-ketosteroids, is assisted by estimation of the neutral 3-beta fraction, which becomes the predominant isomer in most cases of adrenal cancer,[246] and by the response of the 17-ketosteroid level to cortisone therapy.[247] Cortisone administration normally inhibits pituitary ACTH production, and will result in reduction of secretory activity of adrenal hyperplasia but not of tumors, with a resultant fall toward normal in urinary androgens in the former instance. The suppressive effects of cortisone on estrogen production by the adrenal cortex[248] are also of great value in the treatment of estrogen-dependent metastatic mammary carcinomas[161,249,250] to supplement oophorectomy[251] and appear to result in therapeutic results equal if not superior to those noted after total adrenalectomy.[252,253] Several groups of workers have now reported the existence of biologically active estrogens in the urine of postmenopausal and surgically castrated female patients with mammary carcinoma,[248,254] which can be suppressed only in the latter type of patient by use of therapeutic doses of cortisone or by total adrenalectomy. Cortisone is not metabolized to estrogenic substances according to present information,[244] but is converted to a minor extent to androgenic 17-ketosteroid metabolites.[255] Perhaps as a result, its adrenal-suppressive effect has been of somewhat less striking value in the treatment of relapses of metastatic, androgen-dependent prostatic cancer after castration or estrogen therapy or both[256] than in mammary carcinoma.

Abnormal proteins and pigments. Urinary Bence-Jones protein represents one of the earliest noted and still one of the most specific alterations occurring in patients with cancer, usually those with multiple myeloma but at times with other types of osseous neoplasms. The method of estimation developed by Jacobson is recommended for the recognition of these abnormal proteins, whose presence may be masked by albuminuria resulting from the renal disease associated with chronic Bence-Jones protein in the urine (myeloma kidney).[257] Melanin pigment may or may not occur in the urine of patients with metastatic melanoma, depending perhaps on the extent to which two melanin-forming enzymes are retained by the neoplasm.[258,259]

Metabolism of Patients with Cancer

Fall in serum albumin in patients with cancer reflects the depletion of tissue protein and is accentuated by the formation of pleural or ascitic exudates, which remove additional amounts of albumin from that circulating in the vascular system.[260] Mider[261] has reviewed much of the pertinent work, largely carried on by him and his collaborators, concerning the role of the tumor as a "trap" for nitrogenous nutrients. Positive nitrogen balance can be maintained in most

*From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the departments of Medicine and Biochemistry, Boston University School of Medicine.

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†Associate professor of medicine, Boston University School of Medicine; associate member, Evans Memorial Hospital; associate visiting physician, Massachusetts Memorial Hospitals.

‡Professor of biochemistry, Boston University School of Medicine.

§Instructor in biochemistry, Boston University School of Medicine.

¶Assistant professor of biochemistry, Boston University School of Medicine.

cases during a large part of the terminal wasting period, with an apparently excessive flow of intracellular constituents such as nitrogen, phosphorus and potassium into the tumor.[262,263]

Extensive wasting of normal tissues accompanies the growth of some but not all human cancers, patients varying widely in the amount of fat and muscle atrophy. Patients with active cancer growth may have elevated basal metabolic rates without increase in protein-bound iodine in the serum or elevated thyroid uptake of radioactive iodine. Successful antitumor therapy will reduce the caloric expenditure to normal, as well as normalizing the utilization of nutrients.[263] The body fat of some patients with cancer continues to decrease during forced feeding of high-calorie diets, unlike the rapid sparing action of repletion on fat depots observed in the Minnesota studies of severe undernutrition.[264] Lipemia is a frequent late manifestation of cancer both in man and in animals.[261,265] An unusual demand on adipose-tissue stores in cancer may result from excessive requirements for acetyl groups derived from fatty-acid oxidations, engendered by the metabolic inefficiency of glycolysis in furnishing energy for tumor cells.[88] Excessive cancer mortality has been shown to accompany obesity.[266] Undernutrition reduces the frequency of many experimental tumors and, if sufficiently severe, may delay mortality from established neoplasms.[266] Starvation has been shown to reduce the mitotic activity of normal skin,[267] whereas increased dietary fat intake stimulates spontaneous mammary adenocarcinoma and carcinogen-induced cutaneous carcinomas, but not leukemias.[266] Caloric restriction may affect tumor prevalence through hormonal factors since breast cancer develops in susceptible castrate female rats or mice, regardless of the nature of the diet, if a constant diethylstilbestrol supplement is administered.[268,269] Nutritional factors are particularly important in maintenance of secretion of glycoprotein hormones such as gonadotrophins from the adenohypophysis.[270]

In addition to trapping of inorganic constituents tumor tissue probably depletes the host of vitamins,[271] especially when food intake or bowel function is impaired. Because of the increasing mass and the rapid catabolism demonstrable in some tumors, abnormally great destruction of endogenous steroid hormones may also occur.[161] In addition to the degenerative activity of liver and kidney, which has been recognized for some years,[272] epithelial tissues and cancers in vitro appear very active in steroid (testosterone and estradiol) metabolism.[273,274] On a per-cell basis, normal cutaneous tissue and mammary carcinoma have the highest metabolic rates, prostatic cancers showing less activity — but still in excess of that present in human liver.[132]

Ambulatory patients with untreated metastatic mammary cancer excrete significantly less androgenic steroids than those of matched age and sex with benign nonendocrine disease.[161] The adrenal cortex appears normally responsive to ACTH in patients with cancer.[275,276] At death, the hypophyses of these and other patients with cancer possess increased basophilic cell counts indicative of active stimulation of adrenocortical secretion, the major source of androgens in females.[277] The relative absence of such metabolites in urine is difficult to explain except on the basis of increased and perhaps abnormal destruction of endogenous steroids. Therefore, the symptomatic and objective palliation of mammary or other cancer by androgen therapy may rest not only on neutralization or suppression of estrogen activity but also on substitution for deficiencies created by the tumor.

Since 1916 a decrease in hepatic catalase activity has been known to be one of the major distant effects of growing tumors on the host. Greenstein[278] has ably summarized the work in this field. Cancer does not have a specific effect on blood catalase, however.[279]

Several groups of investigators have shown that mitotic activity increases in the normal tissues of tumor hosts,[280,281] a phenomenon that has also been noted in pregnancy. Not only is the weight and mitotic index of the liver affected in rats and mice with malignant tumors elsewhere but also the turnover rate of radioactive phosphorus is increased in the liver, spleen and kidneys — but not the small intestine. No humoral factor has yet been identified in these studies, but such a factor accelerating hepatic mitosis has been identified in parabiont rats, 1 member of which had undergone partial hepatectomy.[282] These observations may have significance in elucidating some of the profound symptomatic changes often occurring with active metastatic growth of cancer (anorexia, nausea, weakness and so forth).

The susceptibility of patients with leukemia or Hodgkin's disease to intercurrent infection has long been appreciated by clinicians. Interference with antibody formation has recently been demonstrated in malignant lymphomas.[283,284] Undoubtedly, these neoplasms more than others interfere with the normal function of the lymphatic system in the biogenesis of antibodies; however, rapidly growing transplanted mouse tumors have been shown to be capable of reducing precipitin levels in the host by as much as 60 per cent. Regressing or slowly growing tumors, on the other hand, did not result in significant impairment of titers of induced antibodies.[285] In view of Cannon's demonstration that undernutrition, especially of essential amino acids, cripples antibody production,[286] further work appears necessary to determine whether this important defect in body physiology represents a nonspecific nutritional defect or a cancer-induced shift in amino acid metabolism.[287,288] Passively transferred antibodies are destroyed at an abnormally high rate in tumor-bearing animals.[285]

Hormonal Regulation of Growth

There is an impressive array of evidence of a close etiologic relation between prolonged endocrine stimuli

and growth of malignant tumors in target organs.[25,289,290] In spite of Beatson's early oophorectomies on patients with mammary cancer little conclusive therapeutic application was achieved until Huggins and Hodges[152] demonstrated the value of castration and estrogen administration in prostatic cancer in 1941. In recent years there has been increasing appreciation among clinicians of the dual origin of sex hormones, from the adrenal cortex as well as gonads, and some additional palliation of mammary and prostatic cancer has been achieved by surgical or medical measures designed to interfere with the production of adrenal hormone.[161,249,252,253,291-293] Since the survival of patients with cancer of the prostate has been definitely prolonged by endocrine therapy[294] and patients with mammary cancer often receive objective benefit for months or years,[295] and since endocrine therapy influences other tumors such as cancer of the male breast,[296] every aspect of chemical growth regulation by means of hormones deserves intensive investigation. Some additional comments appear justified here, since of all chemotherapeutic methods yet developed, endocrine treatment carries the least toxicity, benefits the largest number of patients and can be used with relative safety by most practitioners.

Hormonal Stimulus

Simple phenolic hormones such as epinephrine and thyroxine, in spite of their widespread activity in the body, have not yet been definitely implicated either in carcinogenesis or in tumor maintenance in man. Adrenocortical hormones without sex activity and with an oxygen function at C-11, such as hydrocortisone, do not appear to have a direct relation to carcinogenesis, although they may augment epidermal carcinogenesis in mice after local application.[297] Since cortisone and hydrocortisone influence phagocytosis and immunity through actions on macrophages and lymphocytes respectively,[298,299] their presence in physiologic amounts appears to be one of the essential factors conditioning host resistance to neoplasms. Phagocytosis is augmented by 11-oxysteroids, whereas the lympholytic effect of excessive adrenal steroids, which can greatly depress antibody development, has thereby been of great aid in permitting the growth of some transplanted human tumors in animal hosts.[208,209] Although the growth of some animal tumors is inhibited by cortisone[300] the development of metastases may be augmented.[301] In the management of human lymphomas the use of ACTH and cortisone has not been of such general value as other forms of endocrine therapy for mammary and prostatic cancer,[295] perhaps because neoplastic lymphocyte metabolism is insensitive to the inhibitory effects of corticoids.[302]

At present sex hormones are chiefly implicated as cancer stimuli in man and animals,[25,290] as well as thyrotropic and gonadotrophic factors from the hypophysis that are indirectly important in the regulation of the levels of circulating sex steroids.[289] To the best of our knowledge carcinomas of the breast and uterus have not yet been reported in women with long-standing adenohypophyseal insufficiency, although other types of cancer apparently occur in the usual frequency.[303] We are not aware that prostatic carcinoma has been reported in prepuberal castrate males, although nearly every normal man can expect to develop prostatic cancer if he lives sufficiently long.[304]

Source of Stimulus

Although biochemical evidence of altered secretory activity is not yet available, abnormal histologic patterns have been described in the hypophyses of women with mammary carcinoma[277] and in the ovaries of those with mammary and endometrial carcinoma.[305-307] Cortical stromal hyperplasia of the ovary occurs in 80 to 90 per cent of these patients, compared to no more than a third of women dying of nonneoplastic conditions. Moreover, endometrial cancer complicates 10 to 20 per cent of cases of ovarian granulosa-cell and thecal-cell tumors.[308]

Histologic evidence for continued sex-hormone production exists in the gonads of both sexes well into old age. Cortical stromal hyperplasia may be present at any age after the menopause, and normal Leydig cells, with residual spermatogenic activity, are found in the testis of many aged men. In oophorectomized patients with metastatic mammary carcinoma the existence of ovarian cortical stromal hyperplasia indicates a more favorable prognosis than simple atrophy — that is, an endocrine tumor stimulus has thereby been removed.[309] Perhaps as a result of the high frequency of this lesion, prophylactic and therapeutic oophorectomy is associated with an increased survival rate in mammary carcinoma, even when carried out during or after the menopause.[310,311] The clinical concept that ovarian function completely ceases at the menopause must be discarded once and for all, especially with the increasing analytical evidence for biologically active urinary estrogens in this period of life.[248,254] In all probability, only ovulation and cyclic progesterone secretion cease at this time. Mammary carcinoma often appears to be the result of many years' relatively uninterrupted estrogenic activity; in keeping with this concept is the relative infertility of these patients,[312] in spite of normal physical manifestations of estrinization.

As mentioned above, the continued presence of a carcinogen is no longer necessary when malignant growth has been established. The mechanism whereby estrogen therapy benefits so many elderly women with advanced mammary carcinoma cannot be ignored, and has not thus far received an adequate explanation. The younger the patient, the more hazardous such therapy,[295] which may result in stimulation of metastatic growth. Symptomatic exacerbations are relatively common during the first few weeks of treatment, before benefit, and a possible mechanism of action involves inhibition of pituitary gonadotrophin

production. The degree of basophil hyperplasia of the adenohypophysis appears to be altered by sex-hormone therapy in these patients,[277] and it has been suggested that hypophysectomy may be of therapeutic benefit to some.[313] Another possible mechanism of action depends on decreased metastasizability, resulting from increased biochemical differentiation of the tumor, in response to the characteristic mammary-developmental properties of female sex hormones. The degree of tissue differentiation has been shown to exert a controlling influence on transplantability of tissues,[40] a property that closely parallels metastasizability (as described above).

Hypophyseal function appears also to be important in the induction of thyroid and ovarian cancer, judging from extensive epidemiologic data on the increased frequency of the former disease in areas where chronic thyroid insufficiency has resulted from iodine lack[314] as well as experimental information[289]; the frequency of ovarian cancer, unlike that of most other tumors, declines after the menopause.

Hormonal Effects on Cell Enzymes

An important aspect of the growth-promoting action of hormones is their ability to modify the activity of numerous intracellular enzyme systems, often in a stimulating manner. Testosterone therapy, for instance, causes a great rise in prostatic acid phosphatase of castrate dogs and monkeys,[15,315] and increases the activity of arginase, alkaline phosphatase and beta glucuronidase in the kidney (but not the liver) of rats and mice.[316,317] Estrogens markedly heighten uterine beta glucuronidase activity of castrate female mice[138,318] and hepatic glucuronidase activity of mouse strains genetically deficient in this enzyme.[317] The latter strain of mice (C3H) is very prone to mammary carcinoma.[319]

In adrenalectomized rats a considerable decrease occurs in the alkaline phosphatase activity of upper small intestine and renal tubules, which can be restored to normal with desoxycorticosterone.[320] Other studies show that hormonal factors influence hepatic catalase activity[321,322] and aerobic glycolysis of malignant neoplasms in human beings[323] and mouse tissues.[324,325]

Adrenalectomy in rats prevents the formation of hepatomas by azo dyes,[326] a striking observation of the interrelation between hormonal and carcinogenic action on cells. A wide variety of investigations are currently directed at elucidating hormone-enzyme relations.[327,328] Neoplastic human and animal cell enzymes appear to be less readily influenced by hormones than homologous normal cell components. In special circumstances, in which endocrine therapy modifies neoplastic enzyme synthesis, such as that of acid phosphatases from cancer of the breast and prostate, remissions or exacerbations of disease can be induced, depending on the type of compound administered.

Change in the amount of an enzyme with endocrine or drug therapy may also result from enzyme adaptation in response to the stimulus. The enzyme adaptation may be caused not only by processes of natural selection of cell generations but also, as demonstrated by Knox in tissues of a single animal generation, by the tryptophan-peroxidase system in liver.[329,330] In this metabolic system a great increase of enzyme in response to increased substrate concentration (tryptophan) takes place only when adrenocortical function is intact, illustrating another manner in which hormonal action modifies cell activity. Cancer cells readily adapt to new environmental conditions, particularly the cells in the leukemias,[331] and thus make it difficult to attain prolonged chemotherapeutic suppression of the disease.

Hormonal Antagonism

Clinical experience in cancer therapy indicates mutually antagonistic effects of male and female sex hormones. This antagonism may be mediated through the adenohypophysis in part, since both types of steroids inhibit gonadotrophin production, but may also take place peripherally at the target organ or in the tumor. For instance, the metabolism of testosterone by human prostatic tissue in vitro is altered by the presence of estrogens, especially by natural estrogens that radically change the nature of the principal metabolites.[225] Estrogen promotion of growth in the chick oviduct or rat uterus has been quantitatively inhibited by antecedent therapy with folic acid antagonists — an effect reversed by subsequent addition of folic acid.[332] Some evidence has been obtained for an interrelation between vitamin B_{12} and testosterone metabolism.[146,333] Therefore, nutritional factors may participate in the responsiveness of tissues to steroid agents.

Concurrent stimulation of endocrine glands in chemotherapeutic experiments with folic acid antagonists or nitrogen mustards may take place, as a result of the stressing action of these cytotoxic agents on the pituitary-adrenal system.[334] The release of adrenal steroids may potentiate the action of the chemotherapeutic agent, especially on malignant tumors arising from connective or lymphoid tissues, and this possibility should be considered in the interpretation of the therapeutic significance of such studies far more often than it has previously been. A number of the histotoxic manifestations of these agents are not reproducible, in the usual pharmacologic doses, in homologous tumor tissue cultures[335] or in adrenalectomized animals.[336]

Tumor Adaptation

Malignant tumors arising in endocrine-dependent organs frequently lack hormone sensitivity, although metabolism of steroids may still be demonstrable in clinically autonomous neoplasms.[337] Denaturation of receptor enzymes mediating hormone function may

have occurred during the cancerous change, such as may account for the resistance of transplanted lymphosarcoma cells to the inhibitory effects of 11-oxysteroid compounds[302]; adaptation of tumors to growth inhibitors readily occurs, whether these are steroidal or patterned after some essential metabolite. Somewhat longer remissions of disease occur with endocrine control of mammary and prostatic carcinomas than with antimetabolite therapy of leukemias, but this may merely reflect the more rapid mitotic activity of the leukemias, permitting a more rapid selection of resistant cell types. Tumor adaptation is specific for each compound.[6] In tumors resistant to one agent, additional remissions of disease are achieved with other compounds (either steroids or antimetabolites). As in the chemotherapy of infectious diseases like tuberculosis, increasing research is now being directed against combinations of therapeutic substances, which may block different pathways of essential intermediary metabolism, or sequential steps of a single metabolic function.

Spontaneous Remissions

No review of the biochemistry of human cancer can overlook the phenomenon of spontaneous remissions, which have been reported by a number of well qualified observers.[250,338,339] These remissions serve as prima-facie evidence for the delicate nature of the metabolic balance between host and tumor and attest to the likelihood of host defense mechanisms. In some spontaneously regressing transplanted tumors of lower animals, antitumor antibodies have been identified simultaneously with regression.[6,340]

Regression of advanced metastatic cancer was noted many years ago after severe bacterial infections, and prompted Coley to administer mixed bacterial toxins to far-advanced cases of bone sarcoma and metastatic carcinoma; in a small percentage of such apparently hopeless cases, treated for many months with such preparations, unequivocal regression of the tumors was noted, with survival of the patients for many years thereafter.[341] Intratumor injection was practiced in some but not all cases, and severe pyrexial reactions were the rule after each injection, suggesting that antigens may have been released from the tumor, with ultimate establishment of immunity. There is reason to think that the protein structure of some experimental tumors differs antigenically from that of the host,[39] so that the induction of repeated tumor necrosis may stimulate an effective immunologic response. Furthermore, the mode of therapy must have led to a marked endocrine response to stress.[334] A great deal of work was subsequently carried on by Shear and his co-workers,[342] in an effort to identify the tumor-necrotizing factors in bacterial culture filtrates and to separate these from substances highly toxic to the patient. Good evidence was obtained for the cancerolytic action of the toxins on experimental tumors. However, it was not possible to reduce the hazardous side effects of the particular exotoxins studied.

Another form of spontaneous remission frequently occurs in advanced neoplastic disease of the breast, prostate, thyroid gland and ovary. The natural course of these tumors is often characterized by slow and variable progression, a considerable number of patients living with disease for five years or more, even without specific therapy.[294,343,344] The cachexia induced by the tumor may impair hypophyseal secretory activity sufficiently to reduce thyrotropin or gonadotrophin production to abnormally low levels.[345] Also, in mammary cancer, metastasis frequently involves not only the hypophysis and adrenal cortex but also the ovaries. Nature, therefore, may anticipate the surgeon. The frequency with which malignant tumors of endocrine target organs metastasize to endocrine glands suggests that tumor emboli find unusually favorable nidation sites in these areas, as a result of vascular or hormonal factors.

Spontaneous remissions also occur, however, in gastrointestinal, bronchogenic, hematologic and renal neoplasms, in which no simple explanation of the course of events is possible.[346] Intensive biochemical investigation of these cases would perhaps be highly rewarding in explaining why malignant tumors are not more common causes of death than they are at present.

Summary and Conclusions

Aspects of cancer biochemistry that currently appear to be most pertinent to the understanding of the genesis and maintenance of epithelial malignant tumors of man are considered. A selection of topics is made on the basis of their possible application to the prevention, early detection or medical therapy of neoplastic disease.

A critical study of the comparative biochemistry of more than a few isolated enzyme systems of human or animal cancer has not yet been carried out on a per-cell basis, which might reveal additional significant quantitative differences between malignant and differentiated adult epithelium. Cancers appear to follow species-specific patterns of intermediary metabolism, with considerable variation possible from the normal pattern evolved by each species. Extrapolation of results of investigations utilizing animal tumors to human cancer problems, therefore, is valid only when it can be shown that a comparable biochemical system exists in each species. In the past, most investigators have overlooked the necessity of establishing congruence of biochemical mechanisms in their animal material with human tumors. The application of their findings to the immediate and pressing demands of clinical cancer therapy has not often been possible. Application of this principle has been exemplified by the early work of Huggins on endocrine factors regulating prostatic growth and secretion in dog and man, which led to effective palliation of prostatic cancer.

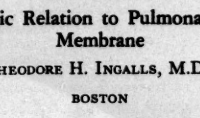
Current intensive investigations of nucleic acid biosyntheses in all likelihood will result in more effective chemotherapeutic agents when a better understanding of human nucleic acid metabolism is achieved. Much further investigation of endocrine factors concerned in the induction as well as the maintenance of human carcinomas also appears to be indicated since the removal or neutralization of such agents has thus far been least detrimental to the patient, and most productive of palliation, of any type of medical therapy.

References

242. Lieberman, S., Dobriner, K., Hill, B. R., Fieser, L. F., and Rhoads, C. P. Studies in steroid metabolism. II. Identification and characterization of ketosteroids isolated from urine of healthy and diseased persons. *J. Biol. Chem.* **172**:263-295, 1948.
243. Dobriner, K. Excretion of steroids in health and disease. *Acta Union internat. contre cancer* **6**:315-328, 1948.
244. Dorfman, R. I., and Ungar, F. *The Metabolism of Steroid Hormones.* 170 pp. Minneapolis: Burgess, 1953.
245. Mason, H. L., and Engstrom, W. W. 17-ketosteroids: their origin, determination and significance. *Physiol. Rev.* **30**:321-374, 1950.
246. Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D. *Functional Endrocrinology from Birth through Adolescence.* 638 pp. Cambridge, Massachusetts: Harvard University Press, 1952. P. 191.
247. Wilkins, L., Gardner, L. I., Crigler, J. F., Silverman, S. H., and Migeon, C. J. Further studies on treatment of congenital adrenal hyperplasia with cortisone. I. Comparison of oral and intramuscular administration of cortisone, with note on suppressive action of compounds F and B on adrenal. *J. Clin. Endocrinol.* **12**:257-276, 1952.
248. Smith, O. W., and Emerson, K., Jr. Urinary estrogens and related compounds in postmenopausal women with mammary cancer: effect of cortisone treatment. *Proc. Soc. Exper. Biol. & Med.* **85**:264-267, 1954.
249. Pearson, O. H., West, C. D., Hollander, V. P., and Treves, N. E. Evaluation of endocrine therapy for advanced breast cancer. *J.A.M.A.* **154**:234-239, 1954.
250. Lemon, H. M. Treatment of metastatic carcinoma. *M. Clin. North America* **38**:1281-1299, 1954.
251. Adair, F. E., Treves, N., Farrow, J. H., and Scharnagel, I. M. Clinical effects of surgical and x-ray castration in mammary cancer. *J.A.M.A.* **128**:161-167, 1945.
252. Huggins, C., and Dao, T. L-Y. Adenalectomy and oophorectomy in treatment of advanced carcinoma of breast. *J.A.M.A.* **151**: 1388-1394, 1953.
253. Kandall, H. T. Evaluation of adrenalectomy in man: physiological changes and effect on advanced neoplastic disease. *Bull. New York Acad. Med.* **30**:278-301, 1954.
254. Dao, T. L-Y. Estrogen excretion in women with mammary cancer before and after adrenalectomy. *Science* **118**:21, 1953.
255. Munson, P. L., Goetz, F. C., Laidlaw, J. C., Harrison, J. H., and Thorn, G. W. Effect of adrenal steroids on androgen excretion by adrenalectomized orchidectomized men. *J. Clin. Endocrinol.* **14**:495-508, 1954.
256. Valk, W. L., and Owens, R. H. Effect of cortisone on patients with carcinoma of prostate. *J. Urol.* **71**:219-225, 1954.
257. Jacobson, B. M., and Milner, L. R. Detection of urinary Bence Jones protein. *Am. J. Clin. Path.* **14**:138-149, 1944.
258. Lerner, A. B., and Fitzpatrick, T. B. Biochemistry of melanin formation. *Physiol. Rev.* **30**:91-126, 1950.
259. Hesselbach, M. L. On participation of two enzyme systems in melanin production in vitro by melanotic and amelanotic tumors of mice. *J. Nat. Cancer Inst.* **12**:337-360, 1951.
260. McKee, F. W., Yuile, C. L., Lamson, B. G., and Whipple, G. H. Albumin and globulin circulation in experimental ascites: relative rates of interchange between plasma and ascitic fluid studied with C^{14} labeled proteins. *J. Exper. Med.* **95**:161-172, 1952.
261. Mider, G. B. Neoplastic diseases: some metabolic aspects. *Ann. Rev. Med.* **4**:187-198, 1953.
262. Waterhouse, C., Fenninger, L. D., and Keutmann, E. H. Nitrogen exchange and caloric expenditure in patients with malignant neoplasms. *Cancer* **4**:500-516, 1951.
263. Fenninger, L. D., Waterhouse, C., and Keutmann, E. H. Interrelationship of nitrogen and phosphorus in patients with certain neoplastic diseases. *Cancer* **6**:930-941, 1953.
264. Keys, A., Brozek, J., Henschel, A., Michelsen, O., and Taylor, H. L. *The Biology of Human Starvation.* 2 vol. 1385 pp. Minneapolis: University of Minneapolis Press, 1950. Vol. 1. Pp. 177-183.
265. Frederick, G. L., and Begg, R. W. Development of lipemia during tumor growth in rat. *Proc. Am. A. Cancer Res.* **1**:14, 1954.
266. Tannenbaum, A. Nutrition and cancer. In *The Physiopathology of Cancer: A treatise for investigators, physicians, and students.* Edited by F. Homburger and W. H. Fishman. 1031 pp. New York: Hoeber, 1953. Pp. 392-437.
267. Bullough, W. S. Effect of restricted diet on mitotic activity in mouse. *Brit. J. Cancer* **3**:275-282, 1949.
268. King, J. T., Casas, C. B., and Visscher, M. B. Influence of estrogen on cancer incidence and adrenal changes in ovariectomized mice on calorie restriction. *Cancer Res.* **9**:436, 1949.
269. Dunning, W. F., Curtis, M. R., and Maun, M. E. Effect of dietary fat and carbohydrate on diethylstilbestrol-induced mammary cancer in rats. *Cancer Res.* **9**:354-361, 1949.
270. Burrows, H., and Horning, E. S. *Oestrogens and Neoplasia.* 189 pp. Springfield, Illinois: Thomas, 1952. Pp. 76 and 77.
271. Bodansky, O., Wroblewski, F., and Markardt, B. Concentrations of ascorbic acid in plasma and white blood cells of patients with cancer and noncancerous chronic disease. *Cancer* **5**:678-684, 1952.
272. Samuels, L. T., and West, C. D. Intermediary metabolism of nonbenzenoid steroid hormones. *Vitamins & Hormones* **10**:251-295, 1952.
273. Ryan, K. J., and Engel, L. L. Interconversion of estrone and estradiol by human tissue slices. *Endocrinology* **52**:287-291, 1953.
274. Wotiz, H. H., and Lemon, H. M. Studies in steroid metabolism. I. Metabolism of testosterone by human prostatic tissue slices. *J. Biol. Chem.* **206**:525-532, 1954.
275. Bonnar, C. D., Fishman, W. H., and Homburger, F. Adrenal cortical responsiveness in patients with cancer and patients with chronic non-neoplastic disease: application of eosinophile uric acid creatinine response test (ACTH) to geriatric patients with chronic diseases. In *Proceedings of the First Clinical ACTH Conference.* Edited by J. R. Mote. 607 pp. Philadelphia: Blakiston, 1950. Pp. 52-54.
276. Nathanson, I. T., Engel, L. L., and Kelley, R. M. Effect of ACTH on urinary excretion of steroids in neoplastic disease. In *Proceedings of the Second Clinical ACTH Conference.* Edited by J. R. Mote. Vol. I. 531 pp. Philadelphia: Blakiston, 1951. Pp. 54-61.
277. Burt, A. S., and Castleman, B. Some histological effects of estrogens and castration on anterior pituitary in women with carcinoma of breast. *Cancer* **6**:236-247, 1953.
278. Greenstein, J. P. Effect of cancer on liver enzymes. *J.A.M.A.* **148**:697-699, 1952.
279. Walter, E. M., Amersbach, J. C., and Rottino, A. Comparison of blood catalase in Hodgkin's and neoplastic disease with that of normal individuals. *Cancer* **5**:375-381, 1952.
280. Kelly, L. S., Payne, A. H., White, M. R., and Jones, H. B. Effect of neoplasia or pregnancy on tissue desoxypentosenucleic acid. *Cancer* **4**:691-696, 1951.
281. Annau, E., Manginelli, A., and Roth, A. Increased weight and mitotic activity in liver of tumor-bearing rats and mice. *Cancer Res.* **11**:304-306, 1951.
282. Bucher, N. L. R., Scott, J. F., and Aub, J. C. Regeneration of liver in parabiotic rats. *Cancer Res.* **11**:457-465, 1951.
283. Larson, D. L., and Tomlinson, L. J. Quantitative antibody studies in man. III. Antibody response in leukemia and other malignant lymphomata. *J. Clin. Investigation* **32**:317-321, 1953.
284. Geller, W. Study of antibody formation in patients with malignant lymphomas. *J. Lab. & Clin. Med.* **42**:232-237, 1953.
285. Wharton, D. R. A., Miller, G. L., Wharton, M. L., Hankwitz, R. F., and Miller, E. E. Effect of tumors on antibody levels in mice. *Cancer Res.* **11**:127-133, 1951.
286. Cannon, P. R. Protein metabolism in relation to resistance to infection. In *Robert Gould Research Foundation Symposia on Nutrition.* Edited by J. B. Youmans. Vol. 2. 370 pp. Springfield, Illinois: Thomas, 1950. Pp. 312-333.
287. Negelein, E. Über die Aufnahme von Aminosäuren durch Gewebschnitte von Tumoren. *Biochem. Ztschr.* **323**:214-234, 1952.
288. Vescia, A., Albano, A., and Iacomo, A. Effect of D (+)-leucine on hydrolysis of glycil-L-leucine in normal and neoplastic tissues. *Nature* (London) **170**:804, 1952.
289. Furth, J. Conditioned and autonomous neoplasms: *review. Cancer Res.* **13**:477-492, 1953.
290. Rawson, R. W. Hormonal control of neoplastic growth. *Bull. New York Acad. Med.* **29**:595-611, 1953.
291. Miller, G. L., and Hinman, F., Jr. Cortisone treatment in advanced carcinoma of prostate. *J. Urol.* **72**:485-496, 1954.
292. Taylor, S. G., III, Li, M. C., Eckles, N., Slaughter, D. P., and McDonald, J. H. Effect of surgical Addison's disease on advanced carcinoma of breast and prostate. *Cancer* **6**:1097-1009, 1953.
293. Harrison, J. H., Thorn, G. W., and Jenkins, D. Total adrenalectomy for reactivated carcinoma of prostate. *New Eng. J. Med.* **246**:86-92, 1953.
294. Nesbit, R. M., and Baum, W. C. Endocrine control of prostatic carcinoma: clinical and statistical survey of 1818 cases. *J.A.M.A.* **143**:1317-1320, 1950.
295. Aub, J. C., and Nathanson, I. T. Neoplastic diseases. *Ann. Rev. Med.* **2**:343-366, 1951.
296. Treves, N. Castration as therapeutic measure in cancer of male breast. *Cancer* **2**:191-222, 1949.
297. Sulzberger, M. B., Herrmann, F., Piccagli, R., and Frank, L. Incidence of epidermal methylcholanthrene tumors in mice after administration of cortisone. *Proc. Soc. Exper. Biol. & Med.* **82**: 673-675, 1953.
298. Gordon, A. S., and Katsh, G. F. Relation of adrenal cortex to structure and phagocytic activity of macrophagic system. *Ann. New York Acad. Sc.* **52**:1-30, 1949.
299. Sayers, G. Adrenal cortex and homeostasis. *Physiol. Rev.* **30**:241-320, 1950.
300. Lemon, H. M., and Smakula, E. Factors affecting hamster sarcoma growth in hamster cheek pouch. *Proc. Am. A. Cancer Res.* **1**:28, 1954.
301. Agnon, M., et al. Cortisone-induced metastases of adenocarcinoma in mice. *Proc. Soc. Exper. Biol. & Med.* **80**:128-131, 1952.
302. Kit, S., and Barron, E. S. G. Effect of adrenal cortical hormones on incorporation of C^{14} into protein of lymphatic cells. *Endocrinology* **53**:1-9, 1953.
303. Archer, B. H. Incidence of peripheral malignancy in Simmonds' disease, with special reference to cancer of breast. *New York State J. Med.* **53**:328, 1953.
304. Hirst, A. E., Jr., and Bergman, R. T. Carcinoma of prostate in women 80 or more years old. *Cancer* **7**:136-141, 1954.
305. Sommers, S. C., Hertig, A. T., and Bengloff, H. Genesis of endometrial carcinoma. II. Cases 19 to 35 years old. *Cancer* **2**: 957-963, 1949.
306. McArthur, J. W. Diseases of reproductive system. *Ann. Rev. Med.* **3**:133-150, 1952.
307. Sommers, S. C., and Teloh, H. A. Ovarian stromal hyperplasia in breast cancer. *Arch. Path.* **53**:160-166, 1952.
308. Willis, R. A. *The Pathology of Tumours.* 992 pp. St. Louis: Mosby, 1948. P. 497.
309. McManus, R. G., and Sommers, S. C. Breast-cancer prognosis and ovarian cortical stromal hyperplasia. *New Eng. J. Med.* **246**: 890-892, 1952.

310. Smith, G. V., and Smith, O. W. Carcinoma of breast: results, evaluation of x-radiation, and relation of age and surgical castration to length of survival. *Surg., Gynec. & Obst.* **97**:508-516, 1953.
311. Horsley, G. W. Carcinoma of breast: radical mastectomy, oophorectomy and hormone therapy. *Virginia M. Month.* **78**:226-231, 1951.
312. Willis, R. A. *The Pathology of Tumours.* 992 pp. St. Louis: Mosby, 1948. P. 227.
313. Laft, R., and Olivecrona, H. Experiences with hypophysectomy in man. *J. Neurosurg.* **10**:301-316, 1953.
314. Hueper, W. C. Environmental cancer. In *The Physiopathology of Cancer: A treatise for investigators, physicians, and students.* Edited by F. Homburger and W. H. Fishman. 1031 pp. New York: Hoeber, 1953. Pp. 730-777.
315. Gutman, A. B., and Gutman, E. B. Adult phosphatase levels in prepubertal rhesus prostate tissue after testosterone propionate. *Proc. Soc. Exper. Biol. & Med.* **41**:277-281, 1939.
316. Kochakian, C. D. Recent studies on *in vivo* and *in vitro* effect of hormones on enzymes. *Ann. New York Acad. Sc.* **54**:534-547, 1951.
317. Fishman, W. H. β-glucuronidase and action of steroid hormones. *Ann. New York Acad. Sc.* **54**:548-557, 1951.
318. Cohen, S. L. Steroidal hormones and tissue β-glucuronidase and esterase. *Ann. New York Acad. Sc.* **54**:558-568, 1951.
319. Morrow, A. G., Greenspan, E. M., and Carroll, D. M. Liver-glucuronidase activity of inbred mouse strains. *J. Nat. Cancer Inst.* **10**:657-661, 1949.
320. Verzár, F. *In vitro* influences of corticosteroids on phosphorylating enzymes. *Ann. New York Acad. Sc.* **54**:716-727, 1951.
321. Adams, D. H. Hormonal factors influencing liver catalase activity in mice: testicular and adrenal factors. *Biochem. J.* **50**:486-493, 1952.
322. Dirscherl, W., Bergmeyer, H-U., and Krüskemper, H. L. Über die Wirkung von Steroidhormonen auf Katalasepräparate verschiedenen Reinheitsgrades. 29. Mitteilung über Sexualhormone, Steroide und Sterine. *Biochem. Ztschr.* **322**:269-279, 1952.
323. Caputo, A. Le modificazioni indotte dal testosterone sulla glicolisi aerobia dei tumori. *Tumori* **38**:275-284, 1952.
324. Dirscherl, W., and Hauptmann, K. H. Analyse der Wirkung von Androgenen und Oestrogenen sowie Cancerogenen auf den Kohlehydratstoffwechsel der Leber. 23. Mitteilung über Sexualhormone und Sterine. *Biochem. Ztschr.* **320**:199-227, 1950.
325. Dirscherl, W., Bergmeyer, H-U., and Breuer, H. Wirkung von Testosteronpropionat auf Atmung, sowie aerobe und anaerobe Glykolyse der Vesiculardrüsen junger und alter Mause *in vitro*. 27. Mitteilung über Sexualhormone, Steroide und Sterine. *Biochem. Ztschr.* **322**:245-262, 1952.
326. Symeonidis, A., Mulay, A. S., and Burgoyne, F. H. Effect of adrenalectomy and of desoxycorticosterone acetate on formation of liver lesions in rats fed *p*-dimethylaminoazobenzene. *J. Nat. Cancer Inst.* **14**:805-818, 1954.
327. Jones, H. W., Jr., and Wade, R. Effect of progesterone on rate of phosphate release from adenosine triphosphate by rat liver homogenates. *Science* **118**:103-107, 1953.
328. Villee, C. A., Loring, J. M., and Wellington, F. M. Estradiol-induced stimulation of citrate utilization in placenta. *Federation Proc.* **13**:314, 1954.
329. Knox, W. E. Two mechanisms which increase in vivo liver tryptophan peroxidase activity: specific enzyme adaptation and stimulation of pituitary-adrenal system. *Brit. J. Exper. Path.* **32**:462-469, 1951.
330. *Idem.* Relation of liver kynureninase to tryptophan metabolism in pyridoxine deficiency. *Biochem. J.* **53**:379-385, 1953.
331. Burchenal, J. H., Armstrong, R. A., and Babcock, G. M. Further studies on mechanism of resistance to therapy in leukemia. *Cancer Res.* **11**:241, 1951.
332. Hertz, R., and Tullner, W. W. Interference with hormonal effects by antivitamins and competition between structurally similar steroid hormones. *Ann. New York Acad. Sc.* **52**:1260-1273, 1950.
333. Pasetto, N., and Pece, G. Influenza della vitamina B12 sulla metabolismo intermedio del testosterone nella ormono terapia del cancro uterino. *Ann. ostet. & ginec.* **74**:759-762, 1952.
334. Selye, H. *The Physiology and Pathology of Exposure to Stress: A treatise based on the concepts of the general-adaptation-syndrome and the diseases of adaptation.* 792 pp. Montreal: Acta, 1950.
335. Antikajian, G., Wright, L. T., Plummer, J. I., and Weintraub, S. Effect of triethylene melamine aureomycin and some 4-amino derivatives of folic acid on tissues *in vitro*. *J. Nat. Cancer Inst.* **12**:269-274, 1951.
336. Dougherty, J. H., and Dougherty, T. F. Acute effect of 4-aminopteroylglutamic acid on blood lymphocytes and lymphatic tissue of intact and adrenalectomized mice. *J. Lab. & Clin. Med.* **35**:271-279, 1950.
337. Lemon, H. M., Wotiz, H. H., and Robitscher, T. Metabolism of testosterone by neoplastic human prostate. *J. Clin. Endocrinol.* **13**:948-956, 1953.
338. Stewart, F. W. Experiences in spontaneous regression of neoplastic disease in man. *Texas Rep. Biol. & Med.* **10**:239-253, 1952.
339. Blades, B., and McCorkle, R. G., Jr. Case of spontaneous regression of untreated bronchiogenic carcinoma. *J. Thoracic Surg.* **27**:415-419, 1954.
340. Ellerbrook, L. D., Rhees, M. C., Thornton, H., and Lippincott, S. W. Complement fixation in animal neoplasia. II. Development and duration of reaction in New Zealand white rabbits carrying Brown-Pearce carcinoma. *J. Nat. Cancer Inst.* **12**:937-946, 1952.
341. Nauts, H. C., Fowler, G. A., and Bogatko, F. H. Review of influence of bacterial infection and of bacterial products (Coley's toxins) in malignant tumors in man. *Acta med. Scandinav.* Supp. **276**:1-103, 1953.
342. American Association for the Advancement of Science. *Approaches to Tumor Chemotherapy: A symposium of papers and discussions on various aspects of tumor chemotherapy, developed from the summer meetings of the Section on Chemistry (C) of the American Association for the Advancement of Science at Gibbon Island, Maryland, 1945-1946.* Edited by F. R. Moulton. 442 pp. Washington, D. C.: American Association for the Advancement of Science, 1947. Pp. 236-284.
343. Daland, E. M. Untreated cancer of breast. *Surg., Gynec. & Obst.* **44**:264-268, 1927.
344. Cole, W. H., Slaughter, D. P., and Majarakis, J. D. Carcinoma of thyroid gland. *Surg., Gynec. & Obst.* **89**:349-356, 1949.
345. Samuels, L. T. Relation of nutrition to anterior pituitary gland. In *Progress in Clinical Endocrinology.* Edited by S. Soskin. 641 pp. New York: Grune & Stratton, 1950. Pp. 509-517.
346. Huth, E. F. Die Bedeutung der sog. Spontanheilungen und Remissionen für die Therapie und Pathogenese der Leukosen und malignen Tumoren. *Ztschr. Krebsforsch.* **58**:524-575, 1952.

MEDICAL INTELLIGENCE



EPIDEMIOLOGY OF RETROLENTAL FIBROPLASIA*

Its Etiologic Relation to Pulmonary Hyaline Membrane

THEODORE H. INGALLS, M.D.†

BOSTON

THE emergence of a new disease is a rare event in the middle of the twentieth century, but for over ten years retrolental fibroplasia has represented a new problem, both clinically and epidemiologically. The challenge to understand causes is not only to be able to prevent the new disease; further knowledge promises to help clarify the vascular basis of ocular and extraocular malformations of the fetus and embryo, and thus to throw light on the etiology and epidemiology of some of the oldest conditions of which there is medical record, the congenital anomalies.

Retrolental fibroplasia could not have been widely prevalent for many years before Terry's[1,2] descriptions in 1942, for the late visual manifestations — often total blindness — are so pronounced that earlier recognition of the severe defect would have been inevitable. In the past decade, however, the condition has come to account for most of the admissions of preschool children to North American institutions for the blind.[3] During the same period Great Britain has fared much better, but the good record there has been interrupted by occasional outbreaks, one of which[4,5] furnished critical evidence that abnormally high tensions of oxygen administered to prematurely born infants contributed to the genesis of the condition.

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†Associate professor of epidemiology, Harvard School of Public Health; associate physician, Children's Hospital; associate editor, *New England Journal of Medicine.*

Epidemiology

Except in New York State (Table 1) retrolental fibroplasia is not generally reportable; hence incidence is poorly known. However, in a survey under-

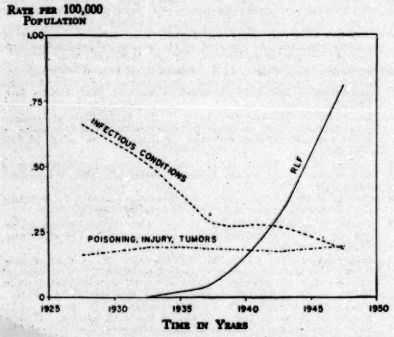

Figure 1. *Trends in Incidence of Blindness in Children by Cause; RLF=Retrolental Fibroplasia (Source: Kerby[1]).*

taken for the National Society for the Prevention of Blindness, Kerby[6,7] found that blindness rates were highest in states having a high prevalence of blindness due to retrolental fibroplasia; two thirds of the new cases of preschool blindness occurring in 1950 were due to this condition. Comparison of figures collected by the Society for 1943 and 1950 revealed an increase of about 50 per cent in the United States between these two periods. Although there was a marked decrease of blindness from other causes, such as injuries, poisoning and infections, the rate of blindness from retrolental fibroplasia had risen steeply in the postwar period.

From another study of 2796 cases of blindness in persons under twenty-one years in 7 states, it was estimated that the average annual incidence of blindness per 100,000 of the population under that age was around 1.5 for many years before 1936.[7] Thereafter, with improved control of infections leading to blindness, — notably venereal disease, — the rate dropped until 1941-45 (Fig. 1). In 1946-50 loss of vision as a result of retrolental fibroplasia increased considerably, and the condition was accounting for over 40 per cent of all blindness occurring in persons under twenty-one years of age. As of 1950, 75 per cent of new cases of blindness were coming from the part of the population under one year of age, but there is little doubt that there has been a precipitous drop in incidence of new cases among infants during the past two years when hyperoxia has emerged as an important determining factor.

Before etiology and influence of age are discussed a few words may be said on the subject of sex and race distributions. Sex is not an important consideration. Silverman and his co-workers[9] found 41 girls and 39 boys in their series of 80 cases of retrolental fibroplasia in New York City. Similarly, in various series reported from Boston, Baltimore and Denver, sex distributions were approximately equal. Racial prevalence is undetermined, but there is no reason to believe that the condition is of biologic rather than social importance.

Table 1. *Blindness from Retrolental Fibroplasia in New York State Reported to State Commission for the Blind According to Year of Report and Age at Time of Report.**

Yr. of Report	Age at Time of Report														Totals
	Patients under 1 yr.	Patients 1 yr. old	Patients 2 yr. old	Patients 3 yr. old	Patients 4 yr. old	Patients 5 yr. old	Patients 6 yr. old	Patients 7 yr. old	Patients 8 yr. old	Patients 9 yr. old	Patients 10 yr. old	Patients 11 yr. old	Patients 12 yr. old	Patients 13 yr. old	
1943			1												1
1944	1	1	2	1											5
1945		4	4	1											9
1946	4	3	4	1	2	1	1								16
1947	2	13	4	4			1								24
1948	4	10	3	3	1	2	1								24
1949	17	21	14		3	1	2	2		1					61
1950	20	28	13	6	4	2	1								74
1951	32	60	18	5	2	2	2	2							123
1952	30	83	20	3	8	5	2	1	1	1					154
1953	52	92	27	4	1	2	3								181
Totals by age at end of 1953	52	122	142	104	67	53	42	28	18	19	11	8	4	2	672

*Reproduced through courtesy of Schlesinger.[8]

Etiology

The action of high-oxygen tensions in the production of retrolental fibroplasia is now established. If

the findings of Campbell,[10] in Melbourne, Australia, Gordon, Lubchenco and Hix,[11] in Denver, Colorado, Patz,[12] in Washington, D. C., and Lanman, Guy and Dancis,[13] in New York, are summed up with disregard of fine points that distinguish one of these studies from another (Table 2 and Fig. 2) the salient fact emerges that over 20 per cent (50 cases) of 247 infants, most of them weighing less than 4 lb., developed severe retrolental fibroplasia in high-oxygen (above 60 per cent) atmospheres whereas less than 2 per cent of 139 premature babies developed the progressive condition under relatively normal atmospheric conditions and when oxygen was used sparingly.

These data accord with the experience of Jefferson[4] and Forrester and Jefferson,[5] who observed 54 patients with retrolental fibroplasia in Manchester, England, during the two years, 1950 and 1951, when oxygen was used in increasingly liberal amounts; 20 of these babies became blind. During the next two years, 1952 through 1953, when oxygen was sparingly used, no cases of blindness occurred although 21 patients with transient changes in the retina were identified.

Unquestionably, environmental hyperoxia in the incubator has determined most of the disease from 1940 to 1950, but the genesis of all retrolental fibroplasia cannot be ascribed to the use of oxygen. A few cases have been reported in infants born at term; at least 5 to 10 severe cases have developed in infants exposed only to the 21 per cent oxygen in air; and early manifestations of disease have been observed

TABLE 2. *Retrolental Fibroplasia in Premature Infants and Oxygen Supply.*

INVESTIGATOR	HIGH OXYGEN SUPPLY*		MODERATE OXYGEN SUPPLY†		LOW OXYGEN SUPPLY‡	
	BABIES AT RISK	CASES OF FIBROPLASIA	BABIES AT RISK	CASES OF FIBROPLASIA	BABIES AT RISK	CASES OF FIBROPLASIA
Campbell[10]	123	23(18.7%)	44	3(6.8%)	14	1(7.1%)
Patz et al.[12]	28	7(25.0%)			37	0(0)
Gordon et al.[11]	60	12(20.0%)	14	4(28.6%)	60	1(1.7%)
Lanman et al.[13]	36	8(22.2%)			28	0(0)
Totals	247	50(20.2%)	58	7(12.1%)	139	2(1.4%)

*About 60-79 per cent.
†About 40-59 per cent.
‡About 20-39 per cent.

despite the cautious use of oxygen as illustrated in the experience of Jefferson[4] and Gordon, Lubchenco and Hicks.[11] There is more to the etiology and epidemiology of retrolental fibroplasia than prematurity and hyperoxia.

CLINICAL RECOGNITION AND AGE AT ONSET

A basic step in the epidemiologic approach to neonatal disability is clinical recognition and dating of onset of the disease being studied — whether it is infectious diarrhea of the newborn or a noninfectious condition like cerebral palsy or retrolental fibroplasia. A simplified and standardized nomenclature for the diagnosis of retrolental fibroplasia is needed, and has been worked out, for this purpose. Thus, the incidence and prevalence of the condition in different clinics of this country and of the world where they are known can be fairly compared, and causation analyzed. Although the 5 structural categories of disease designated by the subcommittee of the National Society for the Prevention of Blindness are wholly adequate for clinical purposes five categories are too numerous for comparative studies of etiology and epidemiology; two are sufficient — one to designate the early and reversible manifestations, and the other for the late and irreversible changes in the fundi. Stage 1 and 2 signs may be grouped together — tortuosity, engorgement, hemorrhage of retinal vessels and patchy edema of the retina. These manifestations may develop or regress rapidly, may escape detection and, indeed, may not even be looked for; certainly, they will not be sought routinely in the future as epidemic retrolental fibroplasia subsides and is replaced by sporadic disease. On the other hand Stages 4 and 5 — growth of neovascular tissue into the vitreous and formation of a grayish membrane in the retrolental space — develop only many weeks and months after earlier manifestations and can hardly escape eventual recognition. The borderline of a two-category classification is evidently to be found around Stage 3 of the five-category clinical classification.

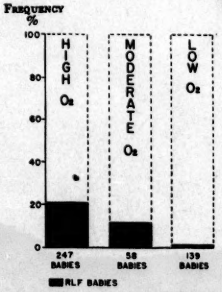

FIGURE 2. *Relation of Retrolental Fibroplasia to Oxygen Tension.*

Several investigators have recognized the necessity of making this distinction between early and late manifestations of retrolental fibroplasia to date the onset of the disease; the data of Lelong and his associates[14] in Paris, France, and Lubchenco and her colleagues,[15] in Denver, Colorado, are made the basis for Figure 3. When retrolental fibroplasia is studied by age at onset — prenatal age being measured from conception rather than birth — a provocative trend emerges: retinal disease takes longer to develop in

younger premature infants than in more mature infants even though the younger babies assuredly have been subjected for longer periods to a high-oxygen atmosphere. Allowing about two weeks as an "incubation period" permitting development of and recognition of regressive signs, the vulnerable stage appeared to be around the eighth month of conceptual age — a time when the fundus is being rapidly vascularized[16]; before seven months of conceptual age early signs of retrolental fibroplasia are not described in the neonatal period.

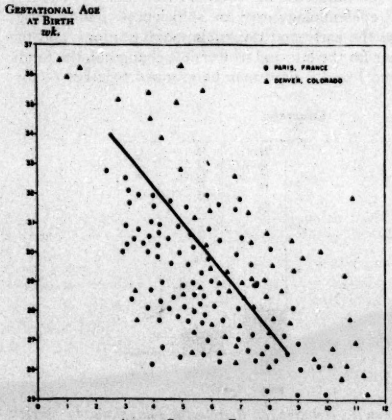

FIGURE 3. *Onset of Retrolental Fibroplasia by Prenatal and Postnatal Ages.*

An interesting epidemiologic question is raised by the data cited. Can one be sure that an adverse environmental agent that can blind a fourth of premature babies exposed to it during the eighth month of conceptual age does not have an occasionally fatal effect or injure organs other than the eye? On biologic principle alone one doubts whether an agent with such a severe morbidity has no mortality. One must at least search for lethal effects of high-oxygen atmospheres, possibly masquerading under some other name and in all probability involving a vital organ — the lungs to judge from the results of fifty years of experimental study of the adverse effects of hyperoxia. At least one such condition is suspect — hyaline-membrane disease of the lung; it has been regarded as originating both in anoxia and in hyperoxia[17] of the lung. The published proceedings of the Pediatric Research Conference on Pulmonary Hyaline Membranes held at Philadelphia in 1953[17] contain a photograph (numbered Figure 29) of an infant laboring within an incubator two hours before death from hyaline-membrane disease — a death that is indistinguishable, clinically, from death due to suffocation and oxygen want. The signs are those of cyanosis and air hunger manifested by tugging of the sternum despite — or perhaps because of — large amounts of oxygen in the incubator; the infant is drowning in his pulmonary exudate. As with retrolental fibroplasia pediatric opinion has been divided on whether the evidence more strongly implicates the operation of hyperoxia or anoxia. However, various investigators of the past[18,19] and selected portions of the vast experience of aviation medicine[20] show that the basic biologic problem has long been settled — that both etiologic positions are correct and that the crux of the problem lies in the fact that anoxia may be induced by many mechanisms, of which atmospheric hyperoxia, paradoxically enough, is one.

For the better part of a century it has been known that prolonged high concentrations of oxygen ultimately have a lethal effect on mammals; in 1927 Binger, Faulkner and Moore[18] after producing death of many animals maintained for about a week in high-oxygen atmospheres came to the conclusion that the ultimate consequence of hyperoxia was hypoxia:

> . . . for several mammalian species, the mouse, guinea pig, rabbit and dog, inhalation of commercial oxygen in concentrations greater than 70 per cent of an atmosphere may lead to a train of physiological changes consisting of drowsiness, loss of appetite, loss of weight, dyspnea and cyanosis, usually culminating in death from extreme oxygen want. The cause of the oxygen want is undoubtedly to be sought for in the acute pulmonary changes, to be characterized as a diffuse hemorrhagic edema of the lungs found in all these species.

The sequences leading from excess atmospheric oxygen to pulmonary embarrassment and anoxia were subsequently confirmed in 1940 by Bean and Bohr,[19] who termed this a "paradoxical relationship in which a superabundant supply of oxygen gives rise to effects induced by oxygen want — a relationship which may perhaps be best described as a hyperoxic anoxia." It remained for German investigators to dissect the pathogenic mechanism in detail.[20]

With the great stimulus to studies of oxygenation in Germany provided by World War II, the development of aviation as an engineering science and aviation medicine as a medical science, much information was gathered on the whole subject of oxygen balance, with the extremes of supply considered as parts of a gradient of oxygen concentrations beginning at next to nothing and increasing through the 21 per cent of oxygen in air to the high-oxygen atmospheres attainable in tents and incubators and with masks; due consideration was given to time factors and to qualitative shifts from one atmosphere to another.[20]

After the empirical observation of a high-altitude flyer, Pezzi,[21] that breathing pure oxygen below 26,000 feet produced "inflammatiop and burns of the respiratory tract" an understanding of the effect of high concentrations of oxygen was gradually achieved experimentally; a morphologic basis for this phe-

nomenon was shown by Pichotka[22] to lie in a combination of pulmonary edema, hemorrhage and hyaline membrane formation:

> In animals exposed for a long period . . . the pleural surface of the lungs is mottled with light and dark red areas. This mottling can also be seen on the cut surface from which a foamy substance can be squeezed. [Histologically the most striking features were] wide homogeneous strands along the walls of the alveoli and bronchioles which appear . . . as fibrinous degeneration. In the small bronchi . . . there is an exfoliation and necrosis of the mucous epithelium. The features of this are the same as those described for phosgene poisoning.

Similar changes are shown in the lungs of an adult mouse kept in 95 per cent oxygen concentration (Fig. 4) in comparison with those of a normal animal (Fig. 5).

The fundamental relation of atmospheric hyperoxia to physiologic hypoxia is also revealed in the same monograph by Becker-Freyseng[24] through demonstration of diminished oxygen saturation of the

FIGURE 4. *Lung of Adult Mouse (X300) after Four Days in 95 Per Cent Oxygen (Source: Ingalls et al.[23]). The animal died less than ten minutes after abrupt removal from the high oxygen atmosphere. Note alveolar and vascular congestion and hyalinization (arrows) of bronchiolar mucosa.*

blood and progressive rise of its carbon dioxide content with each day that rabbits are maintained in high concentrations of oxygen:

> On the fifth day three rabbits showed an oxygen saturation of 75.2, 54.1 and 50.9 per cent respectively, in contrast to the initial valves of 88.0, 99.0, and 93.5 percent . . . *The assumption that there is a progressive oxygen deficiency has thus been confirmed.* [An important observation was that the condition of a poisoned animal often] deteriorates rapidly when it is returned to normal air. . . . In this phase of the Lorrain-Smith effect the increased oxygen tension plays a twofold role: It acts simultaneously as a *poison* and as a *therapeutic agent.*

These observations and interpretations seem to supply a satisfactory and harmonious explanation of Szewezyk's report of functional deterioration of the fundus when infants are moved from high oxygen into room air. These and other data, such as the confirmatory studies of Bruns and Shields,[25] tend to dissipate

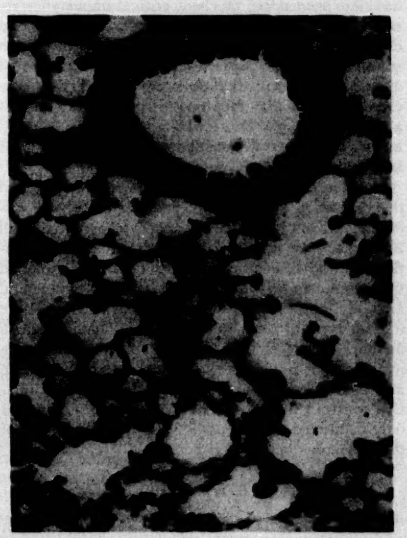

FIGURE 5. *Lung of Adult Mouse (X300) Killed Only for Comparison with the Animal Kept in a High Oxygen Atmosphere.*

incongruities between the work of those who have been approaching hyaline-membrane disease in the neonatal period and retrolental fibroplasia later in the first year of life as manifestations of hypoxia and those who have ascribed these conditions simply to hyperoxia. The logical destination of both groups (like that of engineers starting a tunnel from either end) is a common meeting ground — of balanced oxygen supply; either extreme causes anoxic injury.

In summary it is established that hyperoxia at a steady concentration of 60 to 70 or 80 per cent gives rise to a serious risk of retrolental fibroplasia in the premature baby if he survives. The indications are that hyaline-membrane disease is the counterpart in the human infant of the hemorrhagic pulmonary edema that can be produced experimentally in animals.

The secondary association postulated between the

pulmonary and the ocular disease needs to be confirmed by animal experimentation; the risk of continuing studies on babies in atmospheres high or low in oxygen is prohibitive. Even if it were possible to proceed directly with indicated investigations of newborn babies no conclusive results could be expected because a diagnosis of hyaline-membrane disease is made at autopsy whereas the diagnosis of retrolental fibroplasia is restricted to infants who live — long enough, at least, for the ocular reaction to develop. Much of the basic work on hyperoxia and hypoxia has now been done; much of critical importance remains to be done. Neither oxygenation nor fetal development and response to altered levels of oxygen supply are static processes. At either extreme of oxygen supply critical stresses are reached that may cause death or may give rise to structural defects as a risk of survival. Control rests in avoiding or minimizing both naturally occurring anoxia on one hand and hyperoxic anoxia on the other.

Further clarification of etiologic mechanism and demonstration of a sporadic form of the ocular disease that rests in anoxia unrelated to hyperoxia will assuredly have wide application to other malformations of the conceptus. This is because retrolental fibroplasia can be considered typical of the congenital anomaly, occurring as it does in a fetus born before it has come to term development. The immediate advance that has been made is one in preventive medicine; the implications of the progress being made are for a future advance in public health and a relative control through an improved understanding not only of premature infants but also of adults[26] and of the conceptus before it is born.

References

1. Terry, T. L. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report. *Am. J. Ophth.* **25**:203, 1942.
2. *Idem.* Fibroblastic overgrowth of persistent tunica vasculosa lentis in premature infants: report of cases: clinical aspects. *Arch. Ophth.* **29**:36-53, 1943.
3. Kerby, C. E. *Blindness in Preschool Children.* (Publication No. 113.) 16 pp. New York: National Society for the Prevention of Blindness, 1954.
4. Jefferson, E. Retrolental fibroplasia. *Arch. Dis. Childhood* **27**:329-356, 1952.
5. Forrester, R. M., and Jefferson, E. Oxygen and retrolental fibroplasia: seven-year survey. *Lancet* **2**:258-260, 1954.
6. *Eye Conditions Among Pupils in Schools for the Blind in the United States, 1949-50.* (Report for the Committee on Statistics of the Blind.) (Publication No. 110.) New York: National Society for the Prevention of Blindness.
7. Kerby, C. E. Trends of blindness in children. Presented at the annual meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, October 11-16, 1953.
8. Schlesinger, E. K. Personal communication.
9. Silverman, W. A., Blodi, F. C., Locke, J. C., Day, R. L., and Reese, A. B. Incidence of retrolental fibroplasia in New York nursery. *Arch. Ophth.* **48**:698-711, 1952.
10. Campbell, K. Intensive oxygen therapy as possible cause of retrolental fibroplasia: clinical approach. *M. J. Australia* **2**:48-50, 1951.
11. Gordon, H. H., Lubchenco, L., and Hix, I. Observations on etiology of retrolental fibroplasia. *Bull. Johns Hopkins Hosp.* **94**: 34-44, 1954.
12. Patz, A., Hoeck, L. E., and De la Cruz, E. Studies on effect of high oxygen administration in retrolental fibroplasia. I. Nursery observations. *Am. J. Ophth.* **35**:1249-1253, 1952.
13. Isaman, J. T., Guy, L. P., and Dancis, J. Retrolental fibroplasia and oxygen therapy. *J.A.M.A.* **155**:223-226, 1954.
14. Lelong, M., Rossier, A., LeMasson, J., and Michelin, J. La rétinopathie des prématurés (fibroplasie rétrolentale). *Arch. franç. pédiat.* **3**:550-561, 1951.
15. Lubchenco, L., Boyd, E., and Dressler, M. Growth of prematurely born infants with and without retrolental fibroplasia. Presented at the annual meeting of the American Pediatric Society, Atlantic City, May 7, 1953.
16. Ingalls, T. H., and Purshottam, N. Oxygenation and retrolental fibroplasia. *New Eng. J. Med.* **250**:621-629, 1954.
17. *Pulmonary Hyaline Membranes. (Report of the Fifth M & R Pediatric Research Conference.)* Edited by J. B. Arey. 94 pp. Columbus, Ohio: M & R Laboratories, 1953.
18. Binger, C. A. L., Faulkner, J. M., and Moore, R. L. Oxygen poisoning in mammals. *J. Exper. Med.* **45**:849-864, 1927.
19. Bean, J. W., and Bohr, D. F. Anoxic effects of high oxygen pressure on smooth muscle. *Am. J. Physiol.* **130**:445-453, 1940.
20. Department of the Air Force. *German Aviation Medicine, World War II.* Vol. 1. 648 pp. Washington, D. C.: Government Printing Office, 1950.
21. Pezzi, M. G. Cited by Becker-Freyseng.[24]
22. Pichotka, J. Morphology and morphogenesis of pulmonary changes due to oxygen poisoning. In Department of the Air Force.[20] Pp. 515-525.
23. Ingalls, T. H., Habegger, H., Philbrook, F. R., and Curley, F. J. Unpublished data.
24. Becker-Freyseng, H. Physiological and patho-physiological effects of increased oxygen tensions. In Department of the Air Force.[20] Pp. 493-514.
25. Brunn, P. D., and Shields, L. V. High oxygen and hyaline-like membranes. *Am. J. Obst. & Gynec.* **67**:1224-1236, 1954.
26. Wagener, H. P. Lesions of retina and optic nerve secondary to distant trauma. *Am. J. M. Sc.* **228**:226-235, 1954.

TRIFUR EQUORUM INFECTION IN MAN

J. T. Peters, M.D.*

SODUS, NEW YORK

In connection with an interesting article about animal diseases transmissible to man (the so-called zoonoses)[1] it seems to me of great importance, especially for general practitioners, to know the symptoms of still another zoonosis — *Trifur equorum* infection — that is not mentioned in that article and not even in the newest handbooks of internal medicine. For this reason the disease is often not recognized by the doctor who treats such patients. The possibility that the disease occurs less rarely than one would expect is supported by the following facts: there are a large number of infected horses and mules in the United States, especially in the northern states, according to Hagan[2]; insects, which are well known bloodsuckers in man, are at the same time transmitters of the *T. equorum* infection; and some forms of aplastic anemia of unknown origin have signs and symptoms strikingly similar to those in the following case:

Case Report

The patient, a 45-year-old professor of pathology and hematology at a school of veterinary medicine, had himself made the diagnosis. He was convinced that physicians knew much less about this disease than he did, and had therefore refused all aid and examinations. However, he was persuaded that a comparison of his symptoms with those associated with certain anemias described in man might add to the knowledge of this disease. He consented to be examined with the understanding that certain examinations (such as bone-marrow studies), which he considered unnecessary, would not be included.

He often came in contact with horses suffering from the *T. equorum* infection, but he had never been sick before. His chief complaint was weakness. The present illness had begun 2 years previously, when a skin eruption appeared in the umbilical region that the patient called a "herpetiform exanthema." Soon diarrhea, alternating with constipation, occurred. A few weeks later a slight edema appeared over the whole body but was most evident in the eyelids. There was no albuminuria. Constant weakness, pallor of the skin and severe headaches, usually in the occipital region, developed. After a few months, intervals of relative well-being returned, but recurrent attacks were just as severe.

*Visiting professor of medicine, Louisiana State University School of Medicine.

The urine revealed no pathological findings. The blood was examined many times. The hemoglobin was mostly about 30 vol. per cent (about 4.3 gm. per 100 cc.). The red-cell count was 2,000,000, the mean corpuscular hemoglobin 23 microgm., and the color index 0.8. Normoblasts and megaloblasts were never found. Poikilocytosis and anisocytosis were always present. The white-cell count varied from 1800 to 2600, and the differential count revealed no abnormalities except a relative lymphocytosis. The number of platelets was within normal limits, but many were so-called "giant platelets" (this is perhaps of diagnostic value).

The patient had an intestinal hemorrhage during only one of the exacerbations. There were no abnormal findings in the lungs. The heart showed anemic systolic murmurs over all ostia. The blood pressure was within normal limits. The liver and spleen were not enlarged. Jaundice was absent. Urobilin and urobilinogen were present in normal amounts in urine and blood. Several other examinations would have been of importance but were refused because they would not have improved his condition. As mentioned above, he had made the diagnosis of his disease, which he called by the older name, "pernicious anemia of horses" or "equine infectious anemia," because the symptoms were similar in horses. Proof that his diagnosis was correct was afforded by a test that is used regularly in horses if there is any doubt: the patient injected 1 cc. of his blood intravenously into a young, strong horse, which died of *T. equorum* infection. This crucial test was repeated with the same result in 2 other young healthy horses. He carried out the tests with filtered and unfiltered blood, with identical results. This excluded other diseases not caused by a virus. For nearly 2 years his poor condition remained unchanged. At the beginning of the 3d year, during which I examined him, a slight amelioration appeared, the 1st sign of which was that the intervals between the attacks became longer. Of great importance was the fact that a horse injected with the patient's blood remained healthy. This was repeated in other horses with the same result. (These controls were necessary because there are "healthy" equine carriers.)

However, in spite of the fact that his blood was negative for *T. equorum* at the time I examined him, he considered his prognosis unfavorable because he knew of horses that, after attacks of the disease, apparently became healthy and whose blood remained negative for years. Yet after 10 years or more new attacks developed, in one of which the animal died.

Discussion

From the blood picture, which was not so complete as it would have been with better co-operation of the patient, it is obvious that he had an aplastic type of anemia, which involved the myeloid and erythrogenic tissues but not the platelets. Such forms of aplastic anemias are known to occur in man. In 1938 Downey[3] described this form and reviewed the literature; he called the disease "aplastic anemia without thrombocytopenia." Downey did not mention giant platelets in addition to cases of aplastic anemia without thrombocytopenia. However, some chronic infections are accompanied by giant platelets, and it should therefore be remembered that the *T. equorum* infection in the case reported above showed this sign; the platelets were so strikingly large that not only I but also a specialist in tropical blood diseases, on the first view, confused them with flagellates.

In the future cases of "aplastic anemia without thrombocytopenia" with or without giant cells, which may be absent in certain stages, an intravenous injection of a horse with the blood of the patient should be carried out.

In the chronic form of aplastic anemia in man, hemorrhage is rare, as in the case reported above, in sharp contrast to the well known occurrence of severe hemorrhages in the acute form.

In 1904 the French investigators Carré and Vallée discovered that the disease was caused by a filtrable agent. Later, this virus was called *T. equorum*, which means three-times thief of horses. Another virus from the same genus produces *T. gallinarum* leukemia in fowl. The *T. equorum* is found in blood, urine and feces. Its length is between 18 and 50 millimicrons. It is very resistant to disinfectants, freezing and desiccation. It is spread principally by insects. The chief offenders are the bloodsucking common stable fly, *Stomoxys calcitrans*, and a mosquito, *Anopheles maculipennis*. There are among horses many healthy virus carriers. To detect them, one has to inoculate their blood into other horses. If the first test is negative, it is necessary to inoculate a second horse, because the first test horse can have been a carrier. The use of a second horse makes the chance of error smaller. The same procedure is followed to test the blood of patients with aplastic anemia. If an inoculated test horse is susceptible, fever usually appears within fifteen to thirty days, together with rapid decrease in hemoglobin and red-cell count and an increase of the sedimentation rate and plasma globulins. In horses there are acute, subacute and chronic forms of the disease. Death may occur within a few days in the acute form and within three months in the subacute. Both forms may go into the chronic form, which is interrupted by acute exacerbations, during any of which death may occur. Schalk and Roderick[4] describe a test horse that had several acute exacerbations during the first three years, but then lived in apparently good health for fourteen years; suddenly, this animal died in an acute attack.

Summary and Conclusions

A case of a man suffering from *Trifur equorum* infection is reported and the signs and symptoms are described. It is suggested that cases of suspected *T. equorum* infection be reported to the Laboratory of Infectious Diseases, National Institutes of Health, Bethesda 14, Maryland.

References

1. Steele, J. H. Animal disease problems and public health. *Health News* **30**: November, 1953.
2. Hagan, W. A. *Infectious Diseases of Domestic Animals: With special reference to etiology, diagnosis and biologic therapy.* 655 pp. Ithaca, New York: Comstock, 1943.
3. Downey, H. *Handbook of Hematology.* Vol. 3. 773 pp. New York: Hoeber, 1938.
4. Schalk, A. F. and Roderick, L. M. History of swamp fever virus carrier. *Bull. North Dakota Agric. Exper. Station* **168**:1-14, 1923.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40501

PRESENTATION OF CASE

A seventy-year-old man was admitted to the hospital because of urinary retention.

The patient had always been mentally dull and "somewhat odd," and had never worked. He had been in good health until six months before admission, when he began to lose his appetite and strength. Three weeks before admission, he noted the onset of bilateral upper abdominal, subcostal pain, which appeared on standing and was relieved about twenty minutes after lying down. A week later swelling of the abdomen and ankles developed, bowel movements increased to two or three a day, and he became markedly anorectic and stayed in bed most of the time. Two days before admission, diarrhea, with green, watery stools, began. In the twenty-four hours preceding entry he was unable to void and was so weak that he was unable to get out of bed.

He had had a mild chronic nonproductive cough for many years that had been worse in the last two or three weeks before admission. There was no history of febrile disease, jaundice, bleeding or dyspnea. He denied the use of alcohol or drugs.

Physical examination revealed an apathetic, deaf, moderately dehydrated man. The skin showed slight icterus. Two spider angiomas were identified. The neck veins were slightly distended. The lungs were, in general, hyper-resonant; there was dullness at both bases, and the diaphragmatic leaves were thought to be high. A few rales were heard at both bases. There was some cardiac enlargement. The point of maximal impulse was 10 cm. from the midsternal line. The aortic second sound was greater than the pulmonic. A Grade 2 apical systolic murmur was audible. The abdomen was markedly distended, with periumbilical tympany. There was shifting dullness, and a fluid wave could be elicited. Peristalsis was hyperactive. The liver was questionably palpable and nodular. No masses or tenderness was found. There was ++ pitting edema of the ankles and legs. The prostate was twice the normal size and smooth. There was fecal incontinence.

The temperature was 99.4°F., the pulse 86, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic.

The urine had a specific gravity of 1.030 and gave a trace test for diacetic acid and a positive test for bile; the sediment showed occasional white cells, rare red cells and an unstated number of granular casts per high-power field. The hemoglobin was 11.5 gm. per 100 cc., and the white-cell count 8500. The stool guaiac test was negative. An x-ray film of the chest revealed considerable pulmonary congestion and a high diaphragm. A plain film of the abdomen demonstrated gas-filled loops of small and large bowel, scattered within the abdomen without localized dilatation.

On admission the bladder was catheterized and yielded 125 cc. of urine. A diagnostic abdominal paracentesis disclosed cloudy, amber fluid with a specific gravity of 1.016 and containing 250 white cells (chiefly round cells) per cubic millimeter and occasional red cells. Culture yielded no growth. Laboratory data accumulated during the first two hospital days were as follows: serum bilirubin 1.2 mg. direct and 2.1 mg. total, alkaline phosphatase 4.2 units, nonprotein nitrogen 36 mg., uric acid 3.8 mg., total protein 5.7 gm., albumin 2.5 gm., and globulin 3.2 gm. per 100 cc.; the sodium was 134 milliequiv., potassium 3.6 milliequiv., and chloride 100 milliequiv. per liter. Cephalin flocculation was +++ in twenty-four and ++++ in forty-eight hours, and the prothrombin time was 38 per cent.

The patient was treated with fluid intravenously and was digitalized. Diarrhea continued during the first two hospital days, but then abruptly ceased. On the third hospital day the abdomen was tautly distended, and peristalsis had diminished in activity, with only occasional high-pitched sounds. Proctoscopic examination revealed only an edematous mucosa in the distal 22 cm. of bowel. A Miller-Abbott tube was passed. An x-ray film showed massive distention of the stomach and small and large bowel. A barium-enema examination disclosed apparent obstruction in the splenic flexure, without a demonstrable organic lesion (Fig. 1).

A transverse loop colostomy was done under local anesthesia. Considerable gas passed from the tube inserted into the proximal loop of colon. On the first postoperative day the abdomen remained silent. The patient was disoriented and lethargic. During the next day some respiratory distress was noted, and there was dullness, decreased breath sounds and rales at the right base. Urinary output was low. Edema was now generalized. Bilateral extensor plantar responses appeared. The serum electrolytes were as follows: sodium 125 milliequiv., chloride 87 milli-

equiv., and potassium 5.2 milliequiv. per liter, and nonprotein nitrogen 37 mg. per 100 cc. By the third postoperative day, the patient was comatose. The urinary output remained quite low, and jaundice had notably increased. The serum bilirubin was now 5.3 mg. per 100 cc. total. Intravenous fluid therapy included hypertonic saline solution and 100 cc. of serum albumin a day. On the fourth postoperative day he was deeply comatose, with a decerebrate posture. No corneal reflex could be elicited. The blood sodium was 134 milliequiv., the chloride 100 milliequiv., and the potassium 4.3 milliequiv. per liter; the nonprotein nitrogen was 65 mg., the total protein 5.2 gm., the albumin 1.9 gm., and the globulin 3.3 gm. per 100 cc. On the fifth postoperative day a lumbar puncture revealed clear cerebrospinal fluid under an initial pressure equivalent to 130 mm. and a final pressure equivalent to 100 mm. of water after removal of 6 cc. of fluid. The fluid contained 3 small lymphocytes per cubic millimeter and gave a +++ Pandy test; the total protein was 57 mg. per 100 cc. There was no growth on culture. On the sixth hospital day, the white-cell count was 10,500; the serum sodium was 143 milliequiv., the potassium 4.3 milliequiv., and the chloride 112 milliequiv. per liter, and the nonprotein nitrogen was 90 mg. per 100 cc. The patient was completely unresponsive and had a respiratory rate of 34 with occasional brief periods of apnea. There were coarse rhonchi at both bases. The heart rate was 120. The abdomen was slightly distended. Peristalsis was hypoactive. The legs were somewhat rigid in the extensor position and showed ++++ edema. The position of the arms was unchanged. The temperature gradually rose to 104°F., and he died quietly on the sixth hospital day.

Differential Diagnosis

Dr. Briant L. Decker*: In summary this seventy-year-old man had a six-month history of loss of appetite and strength and a three-week history of progressively increasing pain in the upper portion of the abdomen relieved by lying down, abdominal and ankle swelling, increasing cough, diarrhea, with watery stools, and increasing anorexia and weakness; for twenty-four hours before admission he was unable to void. In the hospital the diarrhea abruptly ceased, intestinal obstruction developed, and a colostomy was necessary. He then gradually became comatose, with abnormal neurologic signs and finally renal failure, and died. Perhaps I had better see the x-ray films.

Dr. C. C. Wang: The x-ray film of the chest taken at the time of admission reveals considerable pulmonary congestion and a fairly high diaphragm; the left border of the heart is poorly seen, but the heart does not appear greatly enlarged. The aorta is quite tortuous. There is probably some fluid in the left pleural cavity. The films of the abdomen on admission show a ground-glass appearance and some increased thickening between the gas-containing loops of small bowel, suggesting the presence of ascites. The outline of the spleen cannot be well traced; the tip of the liver lies at the level of the iliac crest, and the organ is probably somewhat enlarged. Two days later there is rapid accumulation of gas in the stomach and small and large bowel. I do not see any abnormal masses in the abdomen. Although on a barium-enema examination there was some difficulty in retrograde flow of the barium into the colon at the splenic flexure, no definite intrinsic organic lesion can be demonstrated in the colon (Fig. 1).

Figure 1. *Barium-Enema Examination.*
There is considerable accumulation of gas in the small and large bowel, with distention of multiple small-bowel loops. It was not possible to fill the colon with barium proximal to the splenic flexure, although a definite lesion was not demonstrated at this point.

Dr. Decker: I believe that there is not much question about this patient's having had some congestive heart failure; he had an increase in cough, basal rales, distended neck veins, enlarged heart, pulmonary congestion and apparently free fluid in the pleural cavity noted on x-ray examination. He was also thought to be in congestive heart failure by those who saw him, because he was digitalized.

I also believe there is not much question that he had cirrhosis of the liver. In my opinion, the most likely diagnosis of the basic illness is portal cirrhosis, progressing to hepatic coma and renal failure. There was no definite history of hepatitis, and he was in the age group in which hepatitis is somewhat unlikely; however, the subsequent course and findings strongly suggest portal cirrhosis. I think that chronic

*Associate physician, Massachusetts General Hospital.

hepatitis with the six-month history of loss of appetite was probably present. If I can trust the history, he was not an alcoholic and had had no exposure to chemical toxins. It may well be that the cirrhosis developed entirely on a nutritional basis. In support of the diagnosis of cirrhosis, the record states that he had spider angiomas, icterus, ascites, questionable enlargement of the liver and edema of the lower extremities. There was an anemia of considerable degree, which was probably more severe than it appeared to be. The blood smear was not described. The character of the ascitic fluid was consistent with cirrhosis, as was the serum bilirubin, the normal alkaline phosphatase, the greatly reduced albumin (2.5 gm. and later 1.9 gm.), the elevated globulin (3.2 gm.) and the prothrombin time of 38 per cent. The ++++ cephalin flocculation in forty-eight hours, the jaundice and the serum protein level suggest severe liver disease, with parenchymal involvement, as well as beginning liver "decompensation."

On admission the electrolytes were fairly normal. Fluids were given intravenously, and although the record does not say so, the patient was probably given and urged to eat a good diet. We have all seen patients with cirrhosis who have entered the hospital apparently not dangerously ill and who go into coma while on what is thought to be good treatment. I believe the severity of the liver involvement, along with the diarrhea and the operation to which he was subjected, was responsible for the hepatic coma. He did not have a massive paracentesis, nor was there evidence of hemorrhage, either of which might have been a factor in the development of the coma. The diarrhea that he had for four days stopped abruptly, and the abdomen became markedly distended, owing, I believe, to paralytic ileus secondary to impending hepatic coma. No mention is made of the sensorium or neurologic findings at this time.

At the time of admission he had not voided for twenty-four hours, and only 125 cc. of urine was obtained by catheterization. This may have been due to dehydration since the specific gravity was 1.030. No mention was made of albuminuria, and the sediment was not unusual. The urinary output, however, continued at a low level, but it was not until the fourth postoperative day that he began to have evidence of nonprotein nitrogen retention, which continued to increase until he died. I believe the renal failure was most probably due to the acute tubular necrosis caused by the liver failure and congestive heart failure.

The neurologic signs are interesting and, I believe, fit into the picture. I hope that one of the neurologists will discuss them. The first mention we have of definite neurologic abnormality was on the first postoperative day, when the patient was described as being disoriented and lethargic. On the next day he exhibited extensor plantar responses; on the third postoperative day he was comatose, and on the fourth, in spite of an improved electrolyte level, he was in deep coma, with a decerebrate posture. This posture was maintained until death. The cerebrospinal-fluid changes were questionably significantly abnormal: the total protein was only 57 mg. per 100 cc., and the Pandy test was +++. I believe that these neurologic manifestations were part of the hepatic coma although the typical liver "flap" was not mentioned. Foley and Adams* have described abnormal pyramidal-tract manifestations in hepatic coma, and a neurologic consultant has assured me that decerebrate posture may occur in this condition. However, the patient was an elderly man and may well have had a thrombosis in the brain stem or of the basilar artery, either of which would explain the localized neurologic findings.

Another condition I ought to pay some attention to is neoplastic disease, for which I might make a fairly good case. The age, the mode of onset, the change in the bowel habits and the intestinal obstruction, with the presence of a questionably enlarged, nodular liver as well as many of the laboratory findings, are consistent with a diagnosis of cancer in the splenic flexure, with liver metastases. However, the x-ray films do not appear to bear that out, and the stool was reported as guaiac negative. (Certainly, more than one stool examination was done.) He may have had cancer of the pancreas or stomach with liver metastases. If one of these conditions had been present with metastases so extensive as to cause hepatic failure I should have expected a greater degree of jaundice or at least a serum bilirubin with a higher direct percentage. I should also expect the alkaline phosphatase to have had a higher value. The ascitic fluid obtained may be consistent with metastatic disease, but I should expect it to have been more exudative in character; of course, if there had been peritoneal involvement, the character of the fluid would have been greatly different from that reported.

In conclusion it is my opinion that the patient had portal cirrhosis, probably on the basis of chronic hepatitis; hepatic coma; acute tubular necrosis; and arteriosclerotic heart disease, with congestive heart failure.

DR. ROBERT E. SCULLY: Dr. Gardella, will you tell us the opinion on the ward?

DR. JOSEPH W. GARDELLA: I saw this patient during the first three hospital days only; I should like to compliment Dr. Decker on a very shrewd analysis of the data. It is rather disconcerting to have this case simplified so clearly. When I saw the patient I thought the problem was much more complicated. The diagnosis of cirrhosis was at first elusive; but even after establishing this diagnosis, we were taken in by the possibility that the patient had an obstructive intestinal lesion and he was subjected to unnecessary surgery. The subsequent course is not familiar to

*Foley, J. M., and Adams, R. D. Neurological disorder associated with liver disease. In *Metabolic and Toxic Disorders of the Nervous System. (Proceedings of the Association for Research in Nervous and Mental Disease.)* Vol. 32. 604 pp. Baltimore: Williams and Wilkins, 1953. Pp. 198-257.

me. From what I have heard from the house staff, I gather they were all of the opinion that progressive liver failure explained all the findings.

DR. NATHANIEL J. EHRENKRANZ: Did Dr. Decker consider the possibility of hepatoma superimposed on the cirrhosis?

DR. DECKER: No; I did not think the history was long enough for that, although it is a possibility.

CLINICAL DIAGNOSES

Portal cirrhosis.
Intestinal obstruction.
?Metastatic carcinoma in liver.

DR. BRIANT L. DECKER'S DIAGNOSES

Portal cirrhosis.
Hepatic coma.
Arteriosclerotic heart disease.
Tubular necrosis of kidneys.

ANATOMICAL DIAGNOSES

Portal cirrhosis, alcoholic type.
Hyperplasia of astrocytes of brain.
(Hepatic coma.)

PATHOLOGICAL DISCUSSION

DR. SCULLY: At autopsy, as Dr. Decker predicted, the primary disease was in the liver, which was small (weighing 970 gm.), firm and finely nodular. The microscopical appearance was that of an alcoholic cirrhosis. The only unusual feature was the presence of a considerable amount of alcoholic hyaline reticulum in the liver cells despite the fact that there was little or no fat. Typically, when we see this much alcoholic hyalin, fatty vacuolation is also prominent.

We were unable to find an organic lesion in the intestinal tract. The only abnormality here was edema of the large bowel. There were esophageal varices. The spleen, however, was not enlarged. The kidneys were unremarkable. The renal failure must have been of the type that one sees in liver disease without demonstrable structural changes in the kidneys. The heart was of normal size and showed only very slight coronary sclerosis. The lungs were severely congested and edematous, and microscopical examination disclosed an early pneumonia.

Dr. Lapham, will you tell us what was found in the brain?

DR. LOWELL W. LAPHAM: There was no visible atherosclerosis in the vessels at the base of the brain. On the preliminary microscopical sections, there was marked, diffuse hyperplasia of astrocytes in the gray matter, which is consistent with the changes found in hepatic failure.

We cannot correlate the histologic with the clinical findings; we can only say that there was no structural abnormality to account for the abnormal postures that the patient demonstrated. We know that decerebrate posturing with coma occurs in hepatic failure, and we must assume that it is secondary to the metabolic derangement that takes place in the nerve cells secondary to the hepatic disease.

CASE 40502

PRESENTATION OF CASE

A fifteen-year-old girl was admitted to the hospital because of swelling of the maxilla.

An insidious painless swelling of the left maxilla that was unaccompanied by erythema or heat locally was first noticed a month before admission. The mother claimed that various local applications had achieved a transient decrease in size of the swelling. Because there was no real improvement, however, an x-ray film was taken at another hospital that revealed bone destruction of the maxilla with erosion into the maxillary sinus. She was then referred to this hospital.

The past history was noncontributory except for a tonsillectomy and adenoidectomy nine years before admission.

Physical examination demonstrated a painless mass situated just inferior to the malar eminence of the left maxilla, projecting 1 cm. from the surface and measuring 2.5 cm. in diameter. The surface was smooth and unattached to the overlying skin. The buccal mucosa and hard palate were not involved. Many teeth were completely carious up to the alveolar margin.

The temperature was 98.8°F. and the pulse 72.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 16 gm. per 100 cc. and a white-cell count of 9500 and 8700, with 78 per cent neutrophils. The blood Hinton test was negative. X-ray films of the left maxilla disclosed that the entire maxillary sinus was uniformly opaque and expanded, with its lateral, superior and medial walls displaced and thinned. The floor of the orbit was thinned (Fig. 1). No unerupted tooth or crown of a tooth was reported. X-ray films of the chest were normal.

Progress in the hospital was uneventful except for slight elevation of temperature and pulse every afternoon. Penicillin therapy was begun, and on the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARTIN B. LEVENE*: I suppose that I was asked to discuss this case because a year ago I surveyed the lesions in the mandible and maxilla that were seen in this hospital during the past ten years with the hope of being able to differentiate one from another radiographically, and especially of being able to decide from the films whether a lesion was malignant or benign. After reviewing many cases, I was

*Clinical assistant in radiology, Massachusetts General Hospital.

forced to admit that the radiographic appearance alone is often not enough evidence on which to make such a distinction; therefore, it is with some misgivings that I am facing today's exercise. I did find cases in which there were definite characteristics that led me to say that a tumor was malignant, but they were not invariably present.

I should like to present the films in the case under discussion and to point out the features that will help me arrive at a decision. The left maxillary sinus is rather uniformly clouded at all times (Fig. 1). There is no evidence of calcified areas, ossification or zones of radiolucency. However, the sinus is not very dense since a number of things show through it — for example, the superior orbital fissure. If the lesion was very dense it should be obscured. Similarly, a line here appears to represent one of the markings on the calvarium posteriorly. Secondly, the lesion is expanding this sinus. There is rounding of its contour, with upward and lateral displacement of its walls. Even the teeth are slightly displaced downward, and there is very slight inward bulging of the antronasal wall. Thirdly, there are a number of badly carious teeth, especially on the left side adjacent to the area in question. Finally, the turbinates are somewhat swollen and tend to block the nasal cavity. I call attention to this because it may be an explanation for the slight elevation in temperature and pulse; I should not be surprised if the patient had an upper respiratory infection.

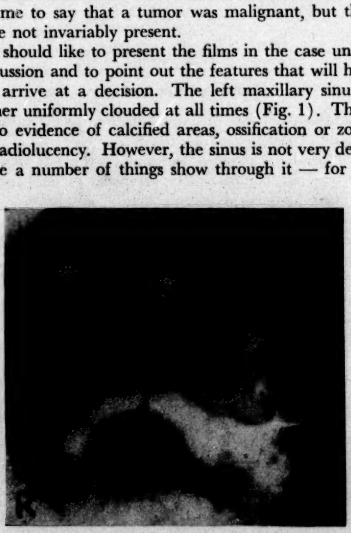

FIGURE 1. *Roentgenogram of the Sinuses. The left maxillary antrum is diffusely expanded and increased in density.*

The protocol is very short, but a few points are worth examining. First of all, in any lesion that is suspected of being a tumor, the age of the patient is important; this girl was fifteen years old, which serves to change and limit the possibilities. The duration of the lesion, I am certain, was understated; lesions that develop insidiously are often present quite a while before they are really brought to anyone's attention, especially if pain is not a feature. The fact that various local applications had reduced the size, I am inclined to discount as the wishful thinking that patients often do.

Among the possibilities for this type of lesion is infection. I think the commonest type of infection in the antrum is sinusitis; in this case it would have been a chronic form of sinusitis. The antrum was clouded, which is a feature of chronic sinusitis, but a number of things are against it — the absence of pain, although this necessarily would not rule it out, and the lack of change in the appearance of the antrum noted in the film taken in the prone position from its appearance in the upright position; there was no evidence of an air-fluid level, and, finally, expansion of the bone is an extremely uncommon manifestation of sinusitis. Similarly, I can discard chronic osteomyelitis largely on the basis of the radiographic appearance. Osteomyelitis in a chronic state in the maxilla is productive of sclerotic changes, possibly sequestra, but it is not usually a uniformly expanding lesion. The more unusual types of infection I shall discard for lack of evidence. The age is against a tertiary lesion of syphilis. Tuberculosis occasionally produces this appearance, but as far as I know there is invariably evidence of disease elsewhere. Fungous infection is usually accompanied by drainage from the sinus and other clinical evidence of disease.

Among the tumors there are a number of possibilities, but I shall limit myself to those that it would be reasonable to expect in this age group. The lesion that is seen in the maxillary sinus much more commonly in children than in adults, although it is a fairly rare occurrence, is fibrosarcoma. In its early stages it is a painless, noninvasive, expanding lesion. The pain apparently does not occur until the lesion breaks through the wall of the sinus. It often causes clouding in the x-ray films because of the blockage of the ostia through which the secretions of the sinus drain, and therefore could produce this type of picture provided it was an early lesion. There is no evidence that it was of such long standing that it should have caused additional changes. I want to put this diagnosis aside temporarily as one of the conditions that have to be considered.

Another lesion of this age group is Ewing's tumor, which is known to occur in the maxillary sinus. It is almost always characterized by pain. The radiographic appearance is somewhat different. It is likely to produce local bone destruction and even periosteal new bone formation — the so-called layering that is sometimes seen with this lesion in other sites.

Osteogenic sarcoma, another malignant process that we must consider, is characterized by destruction, new bone formation and involvement of the surrounding soft tissue due to early penetration of the cortical bone. The absence of pain and soft-tissue involvement and the fact that the overlying skin was freely movable are against that lesion. The limits of an osteo-

genic sarcoma are usually poorly defined in contrast to the clear-cut outline of this lesion.

Carcinoma I can pass over because of the age of the patient.

Of the lesions that arise from the dental structures themselves I should like to mention the adamantinoma. It is usually seen in a patient somewhat older than this, the average age at onset being about thirty years. The youngest patient recorded was six years of age; a fair number of cases occur in the second decade of life. The lesion is variable in form; it may be a single cyst, polycystic or solid. It is much more common (probably four or five times as common) in the mandible than in the maxilla. When it is in the maxilla, it usually involves the antrum, and if it invades the maxillary sinus, it is quite capable of producing this type of expanding picture. It usually does not involve the surrounding soft tissue and is therefore much the type of lesion that I am dealing with here, especially in its solid form. This lesion, therefore, is the second that I should like to place aside for further consideration.

The benign lesions that occur in this location are quite numerous, although not common — for example, myxoma, chondroma and benign giant-cell tumor. Each of these has a fairly characteristic appearance. The myxoma is honeycombed; it never has the uniform appearance seen in this lesion. The chondroma tends to be lobulated, and though it is an expanding lesion, it often has areas of calcification within it. The benign giant-cell tumor characteristically is such an expanding lesion that it separates the teeth in the maxilla; it too is characterized by multiple septums, apparently because it is multicentric, beginning in several places and gradually coalescing.

Osteoma I can rapidly pass by, because of the lack of sufficient density of the lesion. It is usually ivory-like and much more common in the frontal sinus than in the maxillary sinus. Hemangioma I mention because I have seen 1 example of it, — the only one of which I am aware, — but I shall pass it over rapidly.

Lymphoma to the best of my knowledge is not usually seen in this area; however, I have seen reticulum-cell sarcomas here. I think that there would be evidence of disease elsewhere in the body if this were lymphoma, although that is always a dangerous assumption; in many cases in bone there may be an isolated lesion.

Under the heading of tumor I want to talk about ossifying fibroma. This lesion masquerades under many names, probably because of the doubt that exists about its being a true neoplasm — localized osteitis fibrosa, hypertrophic localized osteitis, fibrous osteoma, fibrous dysplasia and fibro-osteoid osteoma. It is said to be somewhat more common in females than in males, and generally is first recognized in the second or third decade of life. The complaint that brings the patient to the physician is usually the appearance of a local asymmetry of the face; occasionally it is impairment or occlusion of the teeth, which occurs as the lesion expands and displaces the molar teeth downward. Another characteristic of this lesion is its ability to compress the antronasal wall, very often with complete obstruction of that side of the nasal passageway and even possibly the opposite side owing to the deviation of the nasal septum. This lesion is classified as benign although it tends to recur if it is partially excised. We have seen 2 cases in this hospital in which pre-existing fibrous dysplasia has undergone sarcomatous change with the development of osteogenic sarcoma. One of these lesions was in the same location as that in the case under discussion. Ossifying fibroma must be seriously considered.

Among a miscellaneous group of lesions are polyps. In the maxillary sinus these arise from myxomatous change in the mucosa. The exciting factor is thought to be nasal allergy. They may become numerous enough and large enough to fill the antrum completely. I shall discard them because there was no history of nasal allergy, and the ethmoid cell partitions were very well mineralized. These usually become partly demineralized and are difficult to see in a patient who has nasal allergy.

Various forms of cysts are seen in the nasal antrum. There are two groups, those of dental origin and those arising primarily in the antrum. The dentigerous or follicular cysts arise from the enamel organ of the tooth and are capable of expanding into the maxilla and producing expansive changes. However, it is always possible to find the crown of a tooth in a dentigerous cyst and I am not able to locate one on these films; therefore, I shall exclude that. The radicular cyst, however, poses a more difficult problem, arising on the basis of infection, apparently as a granuloma at the apex of an infected tooth; central necrosis takes place in the granuloma, and the radicular cyst forms. This lesion can fill the antrum and expand its walls. It too must be put down for serious consideration.

Finally, two other types of cysts are the mucocele and the nonsecreting or subepithelial cyst. The mucocele is a rare lesion in the maxillary antrum. When it occurs, it is usually in the frontal sinus or the ethmoids. The reason it rarely occurs in the antrum is apparently the anatomy of the area. A mucocele arises when the ostium through which the sinus drains becomes blocked and secretions and débris accumulate within the sinus and gradually expand its walls. The maxillary sinus has accessory ostia so that, even if the primary ostium is blocked, there may still be partial drainage and a mucocele does not form. In its place a cystic lesion, which is commonly mistakenly referred to as a mucocele, may arise in the subepithelial layer of the lining membrane. That cyst is not lined by epithelium but by a thin layer of connective tissue. The wall of the cyst is very thin. When the cyst distends sufficiently to fill the antrum, it does not expand the walls but usually ruptures and drains through the ostium or actually may grow out through the ostium and into the nasal cavity.

In closing I am faced with four possibilities: fibrosarcoma, adamantinoma, ossifying fibroma and radicular cyst, all of which could produce this appearance. I should like to ask whether an attempt was made to transilluminate this lesion.

DR. ROBERT E. SCULLY: There is no mention of it in the record.

DR. LEVENE: Transillumination might have been of some help in deciding whether this was a fluid-filled cyst or a solid tumor. The other attempt to arrive at a diagnosis short of biopsy is by aspiration. Often, if the lesion is cystic, it is possible to aspirate some of the fluid. I know of no way in which I can definitely decide whether this was a benign or a malignant lesion, much less what the exact lesion was. On the basis of what I have seen and what is probably the most likely possibility, I shall call this an ossifying fibroma, with the mental reservation that if it was malignant tumor of the antrum, either a fibrosarcoma or an adamantinoma, I shall not be surprised.

CLINICAL DIAGNOSIS

Ossifying fibroma.

DR. MARTIN B. LEVENE'S DIAGNOSIS

Ossifying fibroma.

ANATOMICAL DIAGNOSIS

Radicular cyst of maxilla.

PATHOLOGICAL DISCUSSION

DR. SCULLY: Dr. Taylor, you saw this patient. Would you like to comment?

DR. GRANTLEY W. TAYLOR: When we saw her in the Tumor Clinic our minds worked very much like Dr. Levene's although probably less systematically. We concluded that this was probably a benign tumor, probably fibrous dysplasia or ossifying fibroma, but that it might be a cyst.

We discarded malignant conditions because on examination the patient appeared so well; there was simply a gradual swelling of the cheek. The tumor, on x-ray examination, had not destroyed bone so much as expanded it and just pushed it aside. After a brief period of hospitalization the surgeons decided to explore it.

DR. SCULLY: Dr. David Weisberger, who performed the operation, encountered a cystic structure occupying the maxillary sinus and thinning its anterior wall. The cyst was filled with clear fluid. It was shelled out, and two nearby carious bicuspid teeth were extracted. The specimen received was an already opened cyst, which measured 4 cm. in diameter. Microscopical examination showed the cyst wall to be composed of four layers: a lining of stratified squamous epithelium; a layer of dense fibrous tissue demonstrating severe chronic inflammation; a thin lamina of bone; and an outermost layer of fibrous tissue. The combination of a squamous epithelial lining and chronic inflammation is characteristic of a radicular cyst — the type that arises from an infectious process in the region of the root of a tooth. The microscopical findings are also compatible with a diagnosis of a dentigerous cyst with secondary infection, but as Dr. Levene stated, the x-ray picture rules this out.

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GOD REST YE MERRY

THE concept of Christmas in New England is inextricably bound up with a number of customs, generally pleasant, both local and imported. Some of these are merely ideas or fantasies that have long been considered appropriate to the occasion, such as sleigh rides with jingling bells; the dragging in of fir trees (*Abies balsamea*) by teams of obviously eupeptic ancillary personnel; flushed faces due at least partly to external influences; and groups of mufflered carolers singing carols.

Around a central theme of deep religious feeling a complicated pattern of observances, Christian and pagan, has been woven, all of which have been played nearly to their limit by a wide variety of commercial interests. Thanksgiving as a starting date for the exploitation of Christmas seemed at one time to represent almost an absolute in absurdity, but the opening of the active program on or about Veterans Day — November 11 — shows that no limit is as yet conceded, although it should be apparent that the Christmas spirit can be stretched only so far. But perhaps this is simply an additional effort to bring some meaning to the lost holiday of Armistice Day, intended originally to observe the peace that did not stick. The occasion for celebration was gone but the day remained; a holiday being not easily abandoned, a new reason had to be developed for its existence and, as an extra prop, the Christmas season was advanced to meet it.

Most of the para-Yule observances of this country still derive from English and northern European origins. Santa Claus with his reindeer, undoubtedly jet propelled regardless of the color of their noses; the holly and the mistletoe; the Yule log; the tree and the stocking — all are cherished appurtenances to the glad occasion in America the beautiful. Wooden shoes and similar properties attached to the observance of the day in other climes are not yet recognized as part of a New England Christmas, nor are any special customs that are indigenous to the Antipodes, where, it is said, the Christmas season and midsummer are practically coextensive.

A sort of bookkeeper's ledger page might be devised for Christmas with the debits entered against the credits and a final accounting made to see whether the balance is in black ink or red. To the credit of the Christian world's still most cherished holiday may be entered the unique sentiment that is attached to it; the good feeling that generally prevails, introducing its annual high tide of solidarity; the respect for a group of cherished traditions, and most important, a reaffirmation for many people of that indispensable faith by which men must always live.

On the debit side belong the physical and emotional exhaustion that result from an unparalleled degree of prolonged preparation; the frenzied exchanging of goods that proceeds perhaps less from the heart than

from a compulsive mechanism set in motion by a calculated selling campaign; parenthetically the office party; and in general the making of spurious whoopee that tends to rob the season of its dignity, the celebration of its simplicity and the day of the tranquillity that should accompany any observance of the birth of a spiritual Saviour.

Like the temple of Jerusalem, Christmas might profit from a little house cleaning, but despite the debits in the ledger the final balance stands unalterably on the credit side.

REQUESTS FOR REPRINTS

Society smiles indulgently on hobbyists who collect everything from stamps to automobiles and whose nuisance value is limited to occasional conversational monologues or enthusiastic display of their treasures. Such collectors are quite content to divest themselves of the current medium of exchange for the pursuit of their hobbies and would be amazed to learn that they had rivals in the art of acquisition who are able to amass large quantities of objects without effecting any kind of exchange at all.

The exponents of this technic are the collectors of medical and scientific reprints, who indiscriminately send out hundreds of printed postcards demanding reprints to fill their files of current literature, thereby acquiring in a neat packet the article whose title struck their fancy and providing for themselves a handy and compact source of scientific data.

Hedgpeth, in a paper in the *American Scientist*,* suggests that authors would be more pleased to accede to the requests for reprints if they were written in the form of a personal letter, stating the reason for the application and evincing some sincere and plausible interest in the subject. He expresses the sentiments of most authors whose reprints are in great demand and who are eager to share the results of their investigations or technics or both but who suffer the burden of the financial sacrifice imposed on them by the acknowledgment of all requests.

Physicians and scientists are exceedingly anxious to escape the stigma of being considered mercenary and for that reason are vulnerable to demands involving monetary outlay, both justified and unjustified. These authors are in no position, however, to separate the wheat from the chaff in their harvest of somewhat peremptory postcards suggesting that reprints be sent at their own expense.

Some pharmaceutical firms pay gladly for reprints that pertain favorably to their products, and institutions and clinics also support some of the expenses entailed in the publication of material by members of their staffs — recognizing good publicity. But usually the author is personally responsible for the cost of having his article reprinted.

*Hedgpeth, J. W. On soliciting reprints. *American Scientist* 42:497-499, 1954.

The dissemination of reprints is thus abused by the collector and also by the author who distributes them unsolicited, believing that he is sowing seeds of wisdom in fallow soil or frankly eager to have his achievements recognized as widely as possible. Such authors, magnificent in the bestowal of largesse, promiscuously send their articles to the whole membership of a society. These unsolicited reprints are, of course, frequently relegated to the circular file unless the article is of special interest to the one receiving it or the author is a personal acquaintance; then the recipient is pleased to have been remembered.

The great expense to authors of having articles reprinted and distributed to the many postcard addicts could be eliminated by the establishment of a new custom: that of the ordering of reprints directly from the publisher, who would then mail the reprint and bill the applicant. This business arrangement would relieve the author of the financial burden of the giving away of reprints without recompense as well as that of postage and envelopes, — this charge would be included in the bill, — it would be fair to everybody and perhaps would give added incentive to unhappy writers who have not had reprints made available because of limited personal funds.

YALE SCHOOL OF NURSING

Annie W. Goodrich, recipient of an Sc.D. degree from Mt. Holyoke College, an M.A. degree from Yale University and an LL.D. from Russell Sage College, is primarily and of greatest importance a registered nurse, having received her certificate from New York Hospital in 1892. Superintendent of nursing in various hospitals in the New York area and a member of the faculty of Columbia University, she organized the first Army School of Nursing in 1918. In 1923 she joined the Yale faculty as founder and first dean of the School of Nursing, becoming in addition professor of nursing from 1929 until 1934, in which year she retired.

In view of Dean Goodrich's notable contributions to nursing education the recently announced plan to create in her honor an endowed professorship at the Yale School of Nursing is of more than passing interest. The plan calls for the raising, through alumni and former faculty members, of an endowment fund of $300,000. The professorship thus established will be the first endowed chair in the Yale School of Nursing, which claims the distinction of being the world's first graduate professional school of this nature.

GREEN PASTURES

Since World War II, immigration to the United States has risen to nearly 190,000 yearly, or four times the average number for the preceding fifteen years, according to the Metropolitan Life Insurance Com-

pany.* This is merely a drop in the bucket, however, compared with the years prior to the great depression. During the period of heaviest influx, in fact, — from 1903 until World War I, — the average number of immigrants was over 750,000 annually and six times rose to over a million.

Canada has also experienced a sharp increase in immigration, relatively much greater than that of the United States, because of her smaller population. The annual number of entrants north of the border since the war has been more than 100,000, or a five-fold increase over the 1930 to 1944 experience. This represents a rate of 7.7 per 1000 population, or about six times the rate in the United States.

Half of the recent immigrants to both countries have come from continental Europe; those from the British Isles comprise nearly a third of the number entering Canada and an eighth of those coming to the United States, ostensibly to settle. Of the English-speaking immigrants to each country a considerable number represent a mutual exchange, although emigration from Canada to the United States and elsewhere has always been at a higher rate than that from the United States to Canada and other places. Post-war estimates, in fact, indicate that one person leaves Canada for every two that enter. Many of those that leave represent a remigration to the United States of original immigrants from Europe.

The United States, national pride for the moment disregarded, has been no final haven for much of its population, immigrant or otherwise. During certain years, as from 1932 through 1935, the departures exceeded the arrivals by 139,000, and year in and year out many immigrants return to the lands of their birth or remigrate to other countries. The surprising estimate has been made, in fact, that of the 41,000,000 persons who have come to the land of the free and the home of the brave since its establishment as a nation, as many as 12,500,000 have gone on to fresher fields and perhaps more verdant pastures.

And so the restless human quest for a more abundant life continues.

*Postwar immigration to United States and Canada. *Statist. Bull. Metrop. Life Insur. Co.* 35:8 (September), 1954.

The object of the present communication is to suggest the propriety and expediency of the contribution of a suitable block, of marble or some other suitable material, by the Massachusetts Medical Society, *to the monument now in course of erection at the city of Washington, to the memory of the "Father of His Country."*

Boston M. & S. J., *Dec. 20, 1854*

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held October 20, 1954, it was voted to revoke the registration of Dr. Manford R. Spalding, of Baldwinsville, Massachusetts.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Die Halswirbelsäule: Pathologie und Klinik. By Dr. med. Gerhard Exner, lecturer in orthopedics, Universität Marburg/Lahn. With a foreword by Prof. Dr.h.c.Georg Hohmann, München. 8°, cloth, 140 pp., with 42 illustrations. Stuttgart: Georg Thieme, 1954. DM 21.60 ($5.15). (Distributed by Intercontinental Medical Book Corporation, New York.)

Dr. Exner divides his text on the cervical spine into two parts: general and special. The former discusses normal anatomy, function, clinical considerations, radiologic studies and symptomatology. The latter deals with the various diseases, differential diagnosis and treatment. There is a bibliography of 6 pages.

Die Pathogenese des Icterus Gravis Neonatorum: Ein klinischer Beitrag zur Permeabilitatspathologie. By Dozent Dr. Helmut Patzer, chief physician, Jussuf-Ibraham-Klinik, Univ. Kinderklinik, Jena. 8°, paper, 98 pp., with 5 illustrations. Leipzig: Georg Thieme, 1953. DM 5.40 ($1.25). *(Zwanglose Abhandlungen auf dem Gebiete der Frauenheilkunde, herausgegeben von Professor Dr. Robert Schröder.* Band 16.)

The author discusses the pathogenesis of icterus gravis in the newborn caused by the Rh factor. The study is a survey of the pertinent literature with a bibliography of 9 pages.

Klinische Zytologie: Grundiss der allgemeine Zytologie und der Zytodiagnostik. By Dr. med. H. J. Streicher, assistant, Chirurgische Universitätsklinik Heidelberg: and Dr. med. St. Sandkühler, assistant, Ludolf Krehl-Klinic Heidelberg. With the assistance of Dr. med. Otto A. Roth, assistant, Universitäts-Frauenklinik Tübingen, and Dr. med. W. Schwenkenbecher, leading physician, Internal Division, Kreiskrankenhaus Sulingen/Hann. 8°, cloth, 195 pp., with 58 illustrations. Stuttgart: Georg Thieme, 1953. DM 49.80. (Distributed by Grune and Stratton, New York.)

This monograph on clinical cytology and cytodiagnosis treats the subject in general and its application to diseases of the various systems of the body. Appendixes present various laboratory methods and a cytologic dictionary. The publishing is excellent.

Der Einfluss der antibiotischen und chemotherapeutischen Behandlung auf das morphologische Bild der abheilenden Tuberkulose. By Privatdozent Dr. med. Helmut Lüchtrath, Bonn. 8°, paper, 104 pp., with 42 illustrations. Stuttgart: Georg Thieme, 1954. DM 15.- ($3.55). *(Tuberkulose-Bücherei. Monographien zur Monatsschrift "Der Tuberkulosearzt" herausgegeben von Dr. Rolf Griesbach und Prof. Dr. Otto Wiese.)* (Distributed by Intercontinental Medical Book Corporation, New York.)

This monograph deals with the influence of antibiotic and chemical treatment on the morphologic picture in the healing of tuberculosis. The general chapters present the history of chemical treatment, the latest statistics and the pathological anatomy under the antibiotics. There are sections devoted to general and special pathology. In the special chapters tuberculous meningitis, miliary tuberculosis and caseous pneumonia are discussed. There is a bibliography of 6 pages. The illustrations are excellent.

Schichtbilder von Bronchialveränderungen bei der Lungentuberkulose. By Dr. med. H. Blaha, assistant, Spezial-Lungenklinik in Hemer Westfalen. 8°, paper, 113 pp., with 86 illustrations. Stuttgart: Georg Thieme, 1954. DM 18.- ($4.30). *(Tuberkulose-Bücherei. Monographien zur Monatsschrift "Der Tuberkulosearzt" herausgegeben von Dr. Rolf Griesbach und Prof. Dr. Otto Wiese.)* (Distributed by Intercontinental Medical Book Corporation, New York.)

This special monograph on the stratification of the bronchial changes in tuberculosis of the lungs is based on 47 cases. A comprehensive bibliography of 9 pages is appended to the text. The illustrations are excellent.

Das Bild des Menschen in der Psychiatrie. By Kurt Kolle, professor of psychiatry and neurology, Universität München. 8°, paper, 36 pp. Stuttgart: Georg Thieme, 1954. DM 2.50 ($0.62). (Distributed by Intercontinental Medical Book Corporation, New York.)

This essay is a historical presentation of the progress of psychiatry from the time of Griesinger (1845) to the present.

The Eczemas: A symposium by ten authors. Edited by L. J. A. Loewenthal, M.D. (L'pool), M.R.C.P. (Lond.), D.T.M.&H. (L'pool), lecturer in dermatology, University of Witwatersrand, dermatologist, General Hospital, Johannesburg. 8°, cloth, 267 pp., with illustrations. Edinburgh and London: E. & S. Livingstone, Limited, 1954. $7.50. (Distributed by Williams and Wilkins, Baltimore.)

The authors discuss the histopathology, diagnosis and treatment of eczema and the various types of the disease — allergic, atopic, seborrheic, disseminated and endogenous. The papers by specialists provide a review of the current knowledge of the disease. Bibliographies are appended to the articles. There is a valuable appendix on concentrations and vehicles to be used in patch testing. There is a good index, and the publishing is excellent. The book is recommended for all medical libraries with special collections in dermatology.

Histology. Edited by Roy O. Greep, Ph.D., Dean and professor of dental science, Harvard School of Dental Medicine. With thirteen contributors. 8°, cloth, 953 pp., with illustrations. New York: Blakiston Company, 1954. $15.00.

This is a new type of textbook on histology, with 35 chapters, written by specialists in their fields of medicine. The early chapters deal with general subjects, and the remainder with the systems of the body and the organs. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent. The book is recommended for all collections on the subject.

Fifty Years of Medicine. By Lord Horder, G.C.V.O., M.D., F.R.C.P. 12°, cloth, 70 pp. New York: Philosophical Library, Incorporated, 1954. $2.50.

In this small book Lord Horder has expanded the Harben Lectures he delivered at the Royal Institute of Public Health and Hygiene in December, 1952. The 3 lectures are on the following topics: the birth of scientific medicine; medicine enlarges its boundaries; the present and its future.

Surgical Urology. By R. H. Flocks, M.D., professor of urology and head, Department of Urology; and David Culp, M.D., assistant professor of urology, State University of Iowa College of Medicine. With illustrations by Paul Ver Vais. 8°, cloth, 392 pp., with 118 plates. Chicago: Year Book Publishers, Incorporated, 1954. $9.75. *(A Handbook of Operative Surgery.)*

This small book is a semiatlas of surgery of the genitourinary system, the illustrations providing step-by-step procedures for the various operations. The text is arranged according to organs, and there is a chapter on transurethral surgery. There is a good index, and the publishing is excellent.

Toxicity of Industrial Organic Solvents: Revised in consultation with the Toxicology Committee. By Ethel Browning. Second edition. 8°, cloth, 411 pp., with 53 tables. New York: Chemical Publishing Company, Incorporated, 1953. $8.00.

This book was originally issued as a monograph in the Medical Research Council of Great Britain reports in 1937. This new edition has been thoroughly revised and the bibliography brought up to 1948. Lists of references are appended to the various sections, and there is a good index. The book is an essential reference source.

NOTICES

SOCIETY MEETINGS AND CONFERENCES

December, 1954–April, 1955. Postgraduate Medical Institute. Page 451, issue of September 9.

December, 1954–May, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

December 20–29. Consultation Clinics for Crippled Children in Massachusetts. Page 918, issue of November 25.

December 20, 1954–January 17, 1955. Hartford Medical Society. Page 496, issue of September 16.

December 27. House Officers' Association. Boston City Hospital. Page 958, issue of December 2.

December 21, 1954, January 4 and 18, February 1 and 15, 1955. New England Deaconess Hospital Lectures. Page 993, issue of December 9.

December 21. South End Medical Club. Page 993, issue of December 9.

January 3–May 9, 1955. Postgraduate Seminar in Psychiatry and Neurology. Page 452, issue of September 9.

January 5. New England Cardiovascular Society. Page 993, issue of December 9.

January 7–March 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.

January 7–May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

January 10–15. Course in Care of Atomic Casualties. Page 285, issue of August 12.

February 4 and April 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

February 4 and April 1. New England Society of Anesthesiologists. Page 1054, issue of June 17.

February 7–9. McIntyre-Saranac Conference. Page 410, issue of September 2.

February 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.

February 28. American Orthopsychiatric Association. Page 994, issue of December 9.

March 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.

March 23–26. International Academy of Proctology. Page 876, issue of November 18.

April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 23

THURSDAY, DECEMBER 23

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

FRIDAY, DECEMBER 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xxxi)